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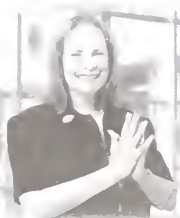
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W O M E N ' S

CATALYST

H E A L T H

FOR

A T

C H A N G E

N I H



Dr. Meera Patel

THE FOLLOWING IS AN INTERVIEW WITH
DR. VIVIAN PINN, NIH ASSOCIATE DIRECTOR FOR
RESEARCH ON WOMEN'S HEALTH. ON
NOVEMBER 19, 1991, DR. PINN WAS APPOINTED
DIRECTOR OF THE NEWLY FORMED OFFICE OF
RESEARCH ON WOMEN'S HEALTH (ORWH).
SHE DISCUSSES SOME OF THE MAJOR ISSUES IN
WOMEN'S HEALTH RESEARCH AND HOW ORWH
IS WORKING TO IMPROVE THE HEALTH OF
AMERICAN WOMEN.

**WHY WAS THE OFFICE OF
RESEARCH ON WOMEN'S HEALTH
(ORWH) ESTABLISHED AT NIH
AND HOW DOES ITS MISSION FIT
INTO THE RESEARCH PROGRAMS
THE INSTITUTES ALREADY HAVE
IN PLACE?**

The office was established in the Office of the Director, NIH, in 1990, in response to a report by the U.S. General Accounting Office (GAO), mandated by the Congressional Caucus on Women's Issues, that women were routinely excluded from medical research supported by NIH. The report also stated that although NIH policy encouraged researchers to analyze study results by gender, the implementation of the policy for including women in research studies was not uniform or consistent. ORWH serves as the focal point for women's health research at NIH. The office was charged with the task of carrying out three major mandates: to strengthen, develop, and increase research for women's health to eliminate gaps in knowledge, and determine the research agenda for women's health; to ensure that women are represented in NIH studies, especially clinical studies; and to increase the number of women in biomedical research careers.

Although the Office of Research on Women's Health was charged with the primary responsibility for accomplishing these goals, this effort is a collaborative project with a shared responsibility with all the NIH institutes. ORWH's task is to strengthen new initiatives, expand ongoing programs, and develop new

ones, when appropriate. Shared funding allows ORWH to accomplish these goals by supporting research by co-funding projects and special initiatives through the various NIH components as well as co-sponsor scientific meetings to assist in determining the scientific agenda.

WHAT ARE SOME OF THE KNOWLEDGE GAPS IN WOMEN'S HEALTH AND HOW ARE THEY BEING ADDRESSED?

There is a need for basic information about normal, healthy development in girls and women across the lifespan as well as on diseases and conditions that primarily affect women, or those that affect both men and women but for which there is less research on women. We do know, for instance, that women tend to have more acute and chronic health problems than men. We also know that certain conditions are more prevalent in women than men, such as Alzheimer's disease, osteoporosis and certain immunologic disorders such as lupus. And although women tend to live longer than men they generally have more illnesses and disabilities than men. Perhaps insights into some of these fundamental questions will yield valuable information about the significance of sex/gender differences in health and disease that can improve our knowledge about the health of both men and women.

Traditionally, the concept of women's health focused on the reproductive system, especially during the childbearing years, without emphasizing the major

non-reproductive diseases and illnesses that affect women. This narrow view of women's health was reflected in the underrepresentation of women in clinical studies of conditions that affect both men and women, but it also was an outgrowth of a biomedical research system that traditionally tended to view health and illness only in terms of the male model. We now know that research results obtained from studies on men do not always apply to women.

In recent years there has been an important shift in the traditional assumptions upon which the research model is based toward the inclusion of more women in research studies as well as a realization that gender differences need to be considered in the design and analysis of research studies. However, more needs to be done in this area. The NIH Office of Research on Women's Health, through a variety of mechanisms, has addressed these concerns by developing a comprehensive, broad-based research agenda for women's health that will expand basic, clinical, and applied research and ensure that women are appropriately represented in medical research studies.

HOW HAS THE NEW, EXPANDED DEFINITION OF WOMEN'S HEALTH MADE AN IMPACT ON SCIENTIFIC RESEARCH?

Because women's health research is no longer viewed solely in terms of reproductive health, the research agenda has broadened considerably to include areas that formerly were not

ULTIMATELY, IT IS HOPED THAT
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always considered relevant to women's health. For example, we know that most women die of the same diseases as men: heart disease, cancer, and stroke, yet women were not always included in research studies on these diseases. Rather than think of diseases as specifically male or female, we've come to a realization that the same disease may have different manifestations that are gender specific and that these manifestations may provide important clues in the effort to improve disease diagnosis, treatment, and prevention. Moreover, research that includes women is producing new discoveries about the fundamental processes of health and disease in both men and women. For instance, we know that women are more vulnerable to autoimmune diseases than men, but we don't know why. Animal studies have shown the importance of hormonal and genetic factors in these disorders. A better understanding of autoimmunity in women can lead to a deeper understanding of the workings of the immune system in both genders.

Thus, in a very real sense, women's health research is changing the paradigm on which scientific research is based. Including women in research studies has generated a growing interest in gender-related research, which will lead to new opportunities to more accurately apply the results of research to greater numbers of people. This expanding field of research is not only attempting to identify gender differences and similarities with regard to health and disease, but also to determine the factors that lead to differ-

ences in health among different ethnic, racial, and other populations of women.

Finally, research strategies for women's health have begun to encompass a multidisciplinary perspective that reflects a growing awareness of the need to integrate women's health research into the framework of scientific research in order to benefit all Americans.

WHY WERE WOMEN NOT INCLUDED IN RESEARCH TRIALS AND WHAT HAS NIH AND ORWH DONE TO ENSURE THAT THEY WILL BE IN THE FUTURE?

There are no clear cut answers that fully explain why women were not included. It's also not clear that they were intentionally excluded, although certainly including women in research studies presented added complications, such as concerns that an experimental treatment or intervention would adversely affect an undetected pregnancy and that the menstrual cycle could confound results. We do know that women were not always included as participants in a number of large, landmark studies and that such exclusion is no longer considered acceptable without good reason.

It is interesting to note that guidelines for the inclusion of women have been in place at NIH since 1986. With the release of the GAO report the guidelines were revised and strengthened to ensure inclusion of women and minorities in NIH clinical studies. In 1993 they were revised again in response to the NIH Revitalization Act, thus making the NIH

policy legally binding. The Act requires that women and minorities are included in clinical research and that clinical trials are designed and carried out to determine if the variables under study affect women and minorities differently from other subjects in the study. Exclusion is allowed if there is a substantial scientific rationale for doing so. Cost is not considered an acceptable justification for exclusion. In addition, outreach activities must be undertaken to recruit women and minorities as study participants.

These requirements were developed to allow investigators the opportunity to gather information on women and minorities early in the research process before interventions are developed so that gender and racial diversity can be taken into account in the final stages of research design and planning. Ultimately, it is hoped that the results from research that includes women and minorities will move closer to closing the gap in scientific knowledge that currently exists with regard to these populations.

HOW IS NIH'S WOMEN'S HEALTH INITIATIVE ATTEMPTING TO ADDRESS THE "KNOWLEDGE GAP" IN WOMEN'S HEALTH?

The Women's Health Initiative (WHI), which was announced in April, 1991, is one of the largest and most ambitious clinical studies ever conducted. The 15-year project will cost more than \$635 million and is scheduled to involve more than 160,000 women ages 50-79, who will be studied at 40 clinical centers

D R .

V I V I A N

P I N N

From the time she was a young child, Vivian Pinn knew she wanted to become a doctor. Growing up with family members who encouraged her served to strengthen her resolve to help others.

"It was the only career I've ever wanted," she explains, "and I feel very fortunate that I had a goal that was important to me personally and professionally."

"My interest in women's health and women's issues evolved over the years as I experienced some of the same situations many women still face today." Pinn is referring to the treatment her mother received from physicians who did not take her complaints seriously, resulting in her death from cancer at the early age of 46. This experience made her more determined to pursue a career in medicine and research to improve the quality of health care for women and minorities. She was the only woman in her medical school class at the University of Virginia, as well as the only minority, and became even more sensitive to how women and minorities were treated in the health care system.

"It was a lonely situation at first, but I learned to manage challenges by viewing them as a source of excitement and opportunity instead of fearing them. With so few women in medicine in the 60s and 70s, I was often the only woman or one of the few women involved in my professional activities. My philosophy then and now is not to let obstacles, no matter how great they may seem, stand in the way of accomplishing your goals. And to do this, one must be

intellectually prepared and dedicated to those pursuits."

Pinn successfully applies this credo in her role as head of the Office of Research on Women's Health at NIH, which among other objectives is committed to increasing the number of women in leadership positions in research and academic institutions. "Today, women make up about 40 percent of entering medical school classes, so they no longer face the same feeling of gender isolation that I did."

Statistics demonstrate that the sheer increase in the numbers of women entering science programs is a sign that progress is being made in the effort to reach professional equality.

But, odds Pinn, there is still the "leadership gap" that exists between men and women in academic and research careers.

"Many talented women scientists hit the 'glass ceiling,' and, as a result, some remain in positions with limited growth potential for long periods of time. Their full participation in the scientific process is seriously diminished and some even decide to leave science entirely. The dual role of women as mothers, providers of long-term care and other family responsibilities,

and as professionals also continues to affect the advancement of women's careers in science.

Today, many women who choose to assume both demanding personal and professional responsibilities serve as important role models for future generations of women. Failure to address the needs of these women seriously jeopardizes their representation in scientific careers. This is an incredible waste of brainpower."

Experts predict that in the coming decades science will depend heavily on minorities and women to fill its ranks, and programs need to be put in place now to attract young students to scientific careers and keep them interested.

"The problem really is a societal one, but it has personal dimensions, too," adds Pinn. "We have to provide the support that women scientists need to succeed. Clearly, we need to fund not just traditional but also non-traditional approaches to career management for women. A fundamental cultural and philosophical change needs to take place, based on the assumption that women can have a balanced life and professional success, too. Indeed, the future of scientific research can benefit from

women achieving their full potential in biomedical research careers."

Developing a future cadre of young women scientists is the focus of several ORWH outreach activities, one of which is aimed at girls in middle school. "For various reasons, many girls at this age lose interest in science or decide it's too hard for them. Over the next few years these girls will be making critical decisions about their future direction; we can't afford to let them give up on a research career."

ORWH supports efforts to overcome identifying the barriers that prevent women from entering science and advancing in their careers and sponsors numerous workshops and seminars on career development. Pinn, who also serves as co-study director of the Women's Health Initiative, often speaks about women's health to groups around the country.

"There's so much interest in women's health and so much activity taking place because of it. Women want to know that NIH is working to improve their health and their lives. I tell them there are many reasons to be encouraged. NIH is directing its policies and resources to provide the scientific data, through biomedical research, that can enable the health care community to better understand, prevent, and treat conditions that affect the health and quality of life for women, their families, and their communities. Even though there are still obstacles to overcome, there has never been a better time for women and women's health." •

around the country. It has been characterized as "the most definitive, far-reaching study of women's health ever undertaken." The WHI will study ways to prevent the most common causes of death and disability among postmenopausal women: heart disease and stroke, cancer, and osteoporosis-related fractures. The WHI should redress some of the inequities that exist with regard to research as well as provide practical information for women and their physicians.

The study has two overall purposes. The first is to prevent cardiovascular disease, breast and colon cancer, and osteoporotic fractures, which are some of the major causes of death, disability, and frailty in older women. There are three components to this trial and women can enroll in more than one. One component will evaluate the effect of a low-fat diet in preventing heart disease and breast and colon cancer. Another will look at the effect of long-term hormone replacement

therapy on heart disease and osteoporosis, and if there is any increased risk of breast cancer. A third arm of the study will evaluate the effect of calcium and vitamin D supplementation in preventing osteoporotic fractures and colon cancer.

Earlier, smaller studies found that some of these interventions may produce favorable results. Randomized, controlled, large scale trials, such as the WHI, provide conclusive data that can be translated to medical practice and to

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everyday life. Possible adverse effects from the interventions will be examined, as will the potential that some have additive effects, such as hormone replacement therapy and calcium supplementation on osteoporosis. Some women will not receive any specific interventions, but will be observed for an extended period of time to identify new risk factors that can predict the development of disease. The second part of the study, the community trial, will evaluate the effectiveness of various approaches in motivating older women to adopt healthy behaviors, such as healthy diets, smoking cessation, physical activity, and regular medical check-ups for early diagnosis of disease.

The WHI represents a major achievement in the effort to provide scientifically sound information for all women regardless of racial, cultural, or economic status. The information and benefits that will be obtained from the WHI studies will likely serve as the basis for disease prevention and health promotion programs that may significantly improve the health and well-being of future generations of women.

**WHAT ARE THE IMPLICATIONS OF
THE GENETIC REVOLUTION FOR
WOMEN'S HEALTH AND WHAT
OPPORTUNITIES LIE AHEAD FOR
SCIENTIFIC ADVANCEMENT OF
POTENTIAL BENEFIT TO WOMEN?**

The recent isolation of genes that predispose for breast and ovarian cancer provides great potential for increasing understanding of these

diseases, and hopefully, for developing more effective prevention and treatments. For these and other diseases that affect women, the search for genes has opened up new areas of research on risk factors, heredity, and the relationship between genetics and the environment. When a disease gene is discovered, scientists have a powerful tool that can ultimately lead to novel and improved approaches to the prevention, detection, and treatment of disease based on more complete knowledge of underlying cellular and molecular mechanisms.

The role of genetic factors, however, must be placed in proper perspective. The development of disease is a complex process and human beings are infinitely unique and varied in their response to their environment. Genetic information must be interpreted in light of individual differences. For instance, not all women with the genes that cause breast cancer—BRCA1 and BCRA2—will develop breast cancer. Those at greatest risk have a strong family history of the disease (a mother or sister with breast cancer). Further research is underway to determine the risk for women with a defective gene but without a family history. Since the majority of women who develop breast cancer do not have a defective gene, genetic susceptibility may be only one of several key factors in cancer development or undiscovered genes may be involved. Researchers continue to search for other genes involved in breast cancer and other cancers in women.

One issue that has raised considerable concern is the use of genetic testing for

both high-risk and normal individuals. At meetings held in April and November, 1996, the Advisory Committee on Research on Women's Health of NIH's Office of Research on Women's Health discussed the issue of genetic testing for breast and ovarian cancer. In summary, the committee recommended that further research should be undertaken before genetic testing can be recommended for all women. High-risk women may receive more benefits from genetic testing, but more research is needed to determine if early medical interventions can reduce the risk of cancer in these women. The committee concluded that genetic testing should be provided in a research environment, which includes informed consent and counseling that addresses the current knowledge about genetic risk, available treatment options, and the limits of testing with respect to preventing disease.

The promise of genetic research is great, but it must be conducted with full knowledge and awareness of the social, ethical, and legal issues that affect the lives of the women who potentially benefit from this work. Research can never be conducted in a vacuum; it is a product of the society that supports it. We must proceed with the hope that genetic information will help us conquer disease by offering unparalleled opportunities to glimpse at and improve our future health. Public education, ethical standards, and societal involvement will help ensure that we use genetic information responsibly and wisely and for the benefit of all men and women.

**AN IMPORTANT MISSION OF
ORWH IS TO INCREASE THE
REPRESENTATION OF WOMEN
IN BIOMEDICAL CAREERS.
HOW IS NIH WORKING TOWARD
THIS GOAL?**

Unfortunately, women still face a number of obstacles that prevent them from entering and advancing in medical research careers. Women tend to select science careers less frequently than men do, and when they do so they often are paid less and experience more underemployment and unemployment than their male colleagues. Many of these problems are entrenched in a system that has been unwilling or unable to accommodate the needs of women with scientific careers. Much of this is due to the fact that society in general and the medical establishment in particular have not valued or encouraged young women to succeed in science nor has the dual role of women as family caregivers and professionals been appreciated. The desire and the drive needed to pursue a career in scientific research has to be nurtured at an early age in the family and in schools where girls have their first exposures to science. Reinforcement from mentors, colleagues, and institutions will offer significant benefits toward helping women stay "in the pipeline" rather than dropping out along the way.

The Office of Research on Women's Health believes that the best means of ensuring that research related to women's health remains a priority into the 21st century is to increase the number of

women in leadership and policy-making positions in research and academic institutions both in the private and public sectors. Recruitment efforts have increased the numbers of women in medical and graduate schools, but comparable progress has not been made in the area of career advancement. In 1992, ORWH held a public hearing and workshop to determine the barriers and recommend solutions to increase the participation of women in scientific careers. As a result, ORWH developed and supported a number of initiatives to implement recommendations made at the workshop.

One important initiative—the ORWH Reentry Program—was developed in 1992 to assist fully trained scientists, the majority of whom are women, reestablish their careers in medical research after taking off time to attend to family responsibilities, such as caring for children. To date, more than 30 reentering scientists have participated in this program, which is supported by 17 NIH institutes. An evaluation of the program revealed that a majority of participants felt that the program had contributed to their long-term career goals. More extensive career follow-up of this and other programs will ensure that we are helping women overcome the barriers that prevent them from full participation and advancement in scientific careers.

**WHAT IS THE FUTURE OF
WOMEN'S HEALTH IN THIS
COUNTRY?**

The future of women's health will be a reflection of the future of this country, and perhaps even the world. Women are the majority gender in this country. In many countries, including our own, women also are on the forefront of social and cultural reform. The role of women in our society has surpassed traditional gender stereotypes, just as women's health research now includes so much more than research on reproductive functions. Truly, we can be hopeful that this trend will continue, but we also must be mindful that true equity means including women of all races and cultures as full participants in medical and behavioral research both as researchers and research subjects.

As we enter the next millennium, and indeed the next phase of women's health in this country, we must direct our efforts to the empowerment of all women by increasing their knowledge and involvement in health care and health research. We must all work for the day when each woman, armed with solid health information based on research, can become her own health care advocate. In the pursuit of these goals, NIH will continue to lead the way in research on women's health so that American women and women the world over can look forward to a healthier and brighter future. •

NCI PROMOTES PROVEN BENEFITS OF MAMMOGRAPHY

CONTROVERSY AROUND THE ISSUE OF WHAT AGE WOMEN SHOULD BEGIN MAMMOGRAPHY SCREENING, PARTICULARLY WHETHER THEY SHOULD BEGIN SCREENING IN THEIR 40S, HAS SOMETIMES OBSCURED AN IMPORTANT FACT: FEWER THAN HALF OF WOMEN OVER 50, AND FEWER THAN 40% OF WOMEN OVER 65, RECEIVE ANNUAL MAMMOGRAMS, DESPITE A PROVEN HEALTH BENEFIT FOR DOING SO. FOR WOMEN IN THEIR 40S, THE RATE IS 34%. IN OTHER WORDS, SCREENING RATES ARE ALMOST AS HIGH AMONG WOMEN FOR WHOM THE SCIENTIFIC EVIDENCE REMAINS UNCERTAIN AS FOR WOMEN IN THE AGE GROUPS FOR WHOM THE BENEFITS OF MAMMOGRAPHY ARE CLEAR.

COMPELLING EVIDENCE: NOT ENOUGH

First, some statistics. It's estimated that 180,200 women will receive a diagnosis of breast cancer in 1997—the majority of them over 50 years old. Breast cancer, like most cancers, is most effectively treated when caught early; mammography, while imperfect, is the best tool we have for detecting breast cancer. Studies have consistently shown a decrease in mortality of about one third among women over 50 who regularly undergo screening mammography. However, data from the 1993 National Health Information Survey indicate that, at the time of the survey, only 46 percent of women over 50—and only 39 percent of women over 65—had a mammogram in the previous year. In the two years before the survey, 65 percent of women 50 to 64 had a mammogram, as compared with 54 percent of women over 65. For women ages 40 to 49, 60 percent had a mammogram during the previous two years.

GIVEN THE MEDICAL BENEFITS, WHY AREN'T MORE WOMEN OVER 50 GETTING MAMMOGRAMS?



Dr. Nancy Breen

"The short answer is, we don't know," admits Nancy Breen, M.D., of NCI Division of Cancer Prevention and Control. Probably, she says, there's no single responsi-

ble factor; however, research shows that certain subgroups of women are less likely to undergo regular screening. These include:

- The relatively small percentage of women who don't have a usual source of health care. "This is probably the group that is worst off," says Dr. Breen. She points out that the vast majority—more than 90 percent—of women who go to mammography clinics are referred by their physicians; in fact, most mammography clinics won't accept a woman without a physician's referral.
- Older women (women older than age 70). "From the literature, physicians tend not to recommend screening to older patients, even though age is a positive predictor for breast cancer," says Dr. Breen. Another factor is that obstetrician/gynecologists are statistically more likely than general practitioners to recommend mammography to their patients, and older women are less likely to be treated by an OB-GYN.
- Lower-income, less-educated women. "Mammography can be expensive; health care can also be expensive, especially a work-up subsequent to a suspicious mammogram," notes Dr. Breen, adding that screening mammography, on the average, costs \$90, while diagnostic mammography costs even more. Forty states have laws requiring third-party payers to cover mammography screening (four others have legislation pending), and since 1991 screening mammograms have been covered by Medicare. (All 50 states currently offer screening mammography through Medicaid;

Studies Show Low Screening Rates Among Older Women



Dr. Otis Brawley

some states have age limits.) One factor that does *not* appear to influence mammography screening rates is race: if you take out factors such as education and socioeconomic levels, the screening rates are remarkably similar across racial and ethnic lines. “[The numbers] are amazingly similar,” says Otis Brawley, M.D., Chief of the NCI Office of Special Populations, but adds, “it’s a shame that the number is so low overall.”

Dr. Brawley also noted that studies to explore ways to encourage mammography screening are ongoing, primarily through extramural studies in the NCI Division of Cancer Prevention and Control.

THE IMPORTANCE OF A CLEAR MESSAGE

The dissemination of a clear public health message about mammography for health professionals and for patients is an important aspect of NCI’s efforts to promote mammography screening.

Staff in the NCI Office of Cancer Communications (OCC) are working on promoting mammography to women, although they are not specifically targeting women over 50. “We want to bring home the message that regular screening mammograms are important for women ages 40 and over,” says Nelvis Castro, Chief of the OCC Health Promotion Branch, but adds, “It’s difficult for us to

target a national media campaign to specific groups.” Her office’s first order of business, she says, is to update existing resources with the new recommendations.

However, she says, “We do plan to work with appropriate federal agencies to emphasize the importance of mammograms for women ages 50 and over. [For this group], the key message will be the same, but the messengers will be different.” For example, she says, OCC will work with publications targeted to senior citizens, such as the American Association of Retired Persons’ *Modern Maturity*, and with the Health Care Financing Administration’s Medicare/Medicaid Program.

Dr. Breen pointed out the importance of sending a clear message about mammography screening to health care professionals, as it is frequently the woman’s physician or health care provider who suggests that she be screened. While obstetrician/gynecologists are already very likely to recommend screening, she says, other health care professionals, such as internists or even specialists in disciplines where the patient populations tend to be older, are in an excellent position to suggest mammography to the women they treat. “All providers need to be encouraged to recommend mammography to their patients,” she says.

Ms. Castro and her office are developing a large-scale communications plan to promote information about breast cancer and screening mammography to women and health care providers. •

Kate Nagy, program analyst, Office of Science Policy, National Cancer Institute.

National Cancer Institute Recommendations on

MAMMOGRAPHY

Should you get a mammogram? Here are the National Cancer Institute’s recommendations:

- **If you’re in your 40s:** Undergo mammography screening for breast cancer every one to two years.
- **If you’re in your 50s:** Undergo screening every one to two years.
- **If you’re at higher than average risk of breast cancer:** Ask your doctor or health care provider whether you should begin screening before age 40, and how often you should be screened.

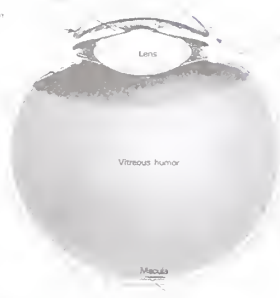
You’re considered at “higher than average risk” if one or more of the following apply to you:

- You’ve had breast cancer before.
- Laboratory evidence has confirmed that you’re carrying a specific mutation or genetic change that increases your susceptibility to breast cancer.
- Your mother, sister, or daughter has had breast cancer, or two close relatives — for example, cousins — have had breast cancer.
- You’ve been diagnosed with another type of breast disease (not cancer but a condition that may predispose you to cancer) on a breast exam, or you’ve had two or more breast biopsies for benign disease, even if no atypical cells were found.
- You have so much dense breast tissue that obtaining a clear reading was difficult on a previous mammographic examination.
- You had your first child at age 30 or older.

For more information about mammography screening, including FDA-approved mammography facilities in your area, contact the National Cancer Institute’s Cancer Information Service at 1-800-4-CANCER. NCI also maintains a comprehensive, consumer-oriented breast cancer resource, including extensive information about screening, on the CancerNet™ web site; the URL is http://concernet.nci.nih.gov/pot_home.htm.

Playing Favorites

Illustration by Dr. H. H. H. H.



OPTIC NEURITIS

MACULAR DEGENERATION

STRIKE WOMEN

MORE FREQUENTLY

Optic neuritis and age-related macular degeneration (AMD)—two eye diseases that can cause serious vision loss and blindness—“play favorites” because they tend to strike women in greater numbers than men. These diseases approach the age spectrum from opposite sides; optic neuritis tends to strike younger people, while AMD affects those primarily over age 60.

Research supported by the National Eye Institute (NEI) is making progress toward finding causes and treatment of both diseases.

OPTIC NEURITIS

It is a silent stalker. About 75 percent of those it attacks are women. It prefers its victims young—about 90 percent of those affected are between 15–45. And when it strikes, it strikes quickly, often leaving lasting, residual damage.

The “attacker”—optic neuritis—is an inflammation of the optic nerve, a bundle of more than one million nerve fibers that carry visual messages from the eye to the brain. Although it is difficult to provide an exact number, it is likely that optic neuritis affects more than 25,000 Americans yearly.

“The usual symptoms of optic neuritis are sudden pain and blurring of central vision, which is used for reading and seeing fine detail,” says Carl Kupfer, M.D., NEI Director. In most cases, optic neuritis affects only one eye.

The disease usually develops in the protective sheath around the optic nerve, which connects the eye with the brain. This protective sheath safeguards the optic nerve from contact with surrounding fluids and tissue. Prolonged or repeated inflammations of the sheath may destroy some of the nerve fibers and

cause a permanent reduction in vision.

Visual loss, which can vary from blurred vision to complete blindness, tends to be sudden and rapid, and may worsen over 7–10 days. Eye movement tends to make the pain worse. The pain often subsides after about a week, although blurred vision can last for months. In many patients, vision improves over a two- to three-month period without any treatment—about 75 percent of those affected have a complete return of central vision, as measured by reading the eye chart.

Most people, however, are left with some visual deficit, usually some permanent residual haziness that can be described as “looking through smoke,” even though outlines of objects are sharp. The recurrence rate of optic neuritis in the same or the other eye is about 15 percent within two years.

Optic neuritis is often a precursor to multiple sclerosis (MS), and there is a close relationship between the two. Multiple sclerosis is a disease of the central nervous system, characterized by extensive damage to the myelin sheaths, or nerve coverings. “More than half of all people with first-time optic neuritis will eventually develop multiple sclerosis,” Dr. Kupfer says. “However, the precise relationship between optic neuritis and multiple sclerosis is not fully understood.”

NEI-supported researchers have discovered that treating optic neuritis with high doses of intravenous steroids, followed by oral steroids, accelerates visual recovery but provides no long-term benefit to vision. Results of the nationwide Optic Neuritis Treatment Trial (ONTT), sponsored by NEI, also showed that oral steroids alone are ineffective in treating optic neuritis, and actually increased the

rate of its recurrence. This unexpected finding resulted in a change in recommended treatment practice. The ONTT scientists also discovered that treating first-time optic neuritis patients with a combination of intravenous and oral steroids lowers their risk of developing MS within the next two years. This finding was the first scientific evidence that intravenous steroids help to delay the progression of MS.

Research on optic neuritis is ongoing. NEI is currently sponsoring a follow-up study to ONTT that continues to assess the effects of steroid treatment for optic neuritis and will determine the natural history of vision in patients who suffer from the disease. The study will also identify risk factors for the development of multiple sclerosis in patients with optic neuritis.

“We are hopeful that this study will help direct future research,” Dr. Kupfer says. “Scientists are working to discover the cause of optic neuritis and develop treatments to mitigate the effects of this disease.”

AGE-RELATED MACULAR DEGENERATION

Cutting a swath of vision loss among older people, age-related macular degeneration is a common eye disease of the macula, a tiny area in the retina that helps produce sharp, central vision required for “straight ahead” activities such as reading, sewing, and driving. A person with AMD loses this clear, central vision. In some cases, AMD advances so slowly that people notice little effect on their vision; however, in others, the disease progresses faster and may lead to a loss of vision in one or both eyes.



Normal vision



Macular degeneration



Cataract

AMD is the leading cause of severe visual impairment and blindness in the United States. It is estimated that AMD already causes visual impairment in approximately 1.7 million of the 34 million Americans over age 65. Studies show that women are more susceptible to AMD, and that people over age 60 are clearly at greater risk of developing AMD than those of other age groups. As the nation's "baby boomers" get older, age-related macular degeneration will become an even more prevalent medical problem.

AMD can be detected through an annual eye exam that includes a dilation of the pupils. It can occur in two forms—a "dry" form and a "wet" form. Scientists are uncertain of the causes of "dry" AMD, in which there is a slow breakdown of light-sensing cells in the macula, subsequently reducing central vision. About 90 percent of people with AMD have this type of the disease. With "dry" AMD, vision loss tends to be more gradual than sudden. Unfortunately, there is as yet no treatment for "dry" AMD.

Although the "wet" form accounts for only 10 percent of those with AMD, it causes 90 percent of all blindness resulting from the disease. As "dry" AMD worsens, new, fragile blood vessels grow beneath and into the macula. These new blood vessels often leak blood and fluid, causing rapid damage to the macula and quickly leading to loss of central vision. Research supported by NEI was instrumental in the development of laser surgery to treat some cases of the "wet" form of AMD. This treatment, performed in a doctor's office or eye clinic, involves aiming a strong light beam toward the new blood vessels and

THE NEI IS CURRENTLY

FUNDING A NUMBER

OF STUDIES TO LEARN

WHAT CAUSES AMD AND

HOW IT CAN BE TREATED

MORE SUCCESSFULLY

destroying them. However, it should be noted that only a relatively small percentage of patients with the "wet" form of AMD are eligible for laser surgery because the new blood vessels may have advanced too close to the fovea, a delicate part of the retina. Despite laser treatment, the disease and loss of vision may progress.

RESEARCH ON AMD

Finding causes of this disease and subsequently safe and more effective treatments is a priority at NEI, which intends to spend approximately \$75 million dollars—22 percent of this year's NEI budget—on all macular degeneration-related research. Of this \$75 million, approximately \$16 million is specifically targeted to researching causes and treatment of AMD.

NEI is currently funding a number of studies to learn what

causes AMD and how it can be treated more successfully:

- Researchers at 11 clinical centers around the country are assessing the aging process, potential risk factors, and quality of life of 4,700 patients. These characteristics may be associated with the development of AMD. "Once such studies have helped us to determine how macular degeneration develops, we might be able to change its course," Dr. Kupfer said. "When we know for certain the risk factors that contribute to development of the disease, we can caution patients to avoid them."
- The same study also includes clinical trials that will help determine the effects of certain vitamins and minerals in preventing or slowing the progress of AMD. In particular, researchers are closely examining whether vitamins C and E, beta-carotene, and zinc can provide the macula with greater protection, thereby preventing or slowing progression of the disease. If dietary supplements prove effective, it would have a huge impact on AMD treatment and reduce the need for low vision services and devices for older Americans. It should be noted that on occasion, seemingly benign nutrients such as vitamins and minerals can be toxic when taken inappropriately, especially vitamins that accumulate in body fat. "When the Age-Related Eye Disease Study is completed within the next five years," Dr. Kupfer said, "we will know if any of these vitamin and mineral combinations will be both effective and safe therapy for macular degeneration."
- A five-year study begun in 1996 is evaluating genetic and environmental

WHY

Women

Should

Be

Concerned

factors related to AMD and examining an underlying hypothesis that genetic factors play a significant role in this complex chronic disease. Participating families include those with both a single case of documented AMD and those where at least two living siblings (or a parent) have documented AMD.

- Other approaches to solving the problem of AMD include laboratory, or basic research. This research includes studies of genetic factors to assess the role of heredity in the development of AMD. NEI scientists are also trying to identify genes that could help rescue the retina; this strategy may help to prevent much of the visual loss from later stages of AMD. Scientists have already successfully placed genes into the retina of laboratory animals, and clinical trials in humans are in the planning phase. Replacing diseased retinal cells with healthy ones is another promising area of research; NEI scientists are working to apply retinal cell transplants to treat retinal degeneration caused by AMD.

“NEI is using existing Federal dollars in the best way possible to research the cause and develop treatments for age-related macular degeneration and a better understanding of eye health care,” Dr. Kupfer says. “The National Eye Institute will continue to devote a significant portion of its annual budget to support research aimed toward learning more about this debilitating disease that affects the lives of millions of Americans.” •

*Michael Coogan, writer/editor,
National Eye Institute.*

Women over 60 need to be aware of another eye disease—

cataracts. Unlike treatment for other serious eye diseases, however, cataracts can be removed in one of the most common and successful surgeries in the United States.

A cataract is a clouding of the eye's lens, which consists mostly of water and protein. This protein is spread throughout the eye, keeping the lens clear and allowing light to pass through. However, as we age, the protein may start to clump together and cloud a small area of the lens. This “clump” is called a cataract. Over time, the cataract may grow larger and cloud more of the lens, making it harder to see. It is after age 60 that most cataracts begin to steal vision.

People with cataracts may at first notice that their vision is slightly blurred, much like looking through a cloudy piece of glass. A cataract

may make light from a sun or lamp seem too bright, causing glare. Colors may not seem as vivid. Glare from oncoming headlights during nighttime driving can become more pronounced. As the cataract enlarges and clouds more of the lens, reading and other normal tasks become harder.

A thorough eye examination can detect the presence of a cataract. Cataracts can be treated with surgery in which the clouded lens is removed and replaced with a clear, plastic lens. More than 1.5 million cataract surgeries are performed in the United States each year and are highly successful in restoring vision.

The National Eye Institute is supporting studies that focus on preventing or controlling cataracts with drugs so that surgery may not be needed in the future. NEI is also evaluating whether certain vitamins and minerals might prevent cataracts or slow their progress. •

PEPI:

REDUCING RISK FACTORS FOR HEART DISEASE

Hearth disease is the leading cause of death and illness for women and men. But unlike men, women usually don't suffer the effects of heart disease until after age 60.

This is thought to be related to women's production of estrogen, which changes with menopause. Estrogen is believed to affect factors that lead to heart disease. If it does, its use during menopause might help women stay healthy and avoid heart disease.

Hormone replacement therapies (HRT) have long been used to treat the symptoms of menopause, such as hot flashes and flushes, sweats, and sleep disturbances. A woman takes an estrogen alone or in combination with another hormone, progestin (progesterone).

Although evidence has accumulated supporting the benefits of HRT, there are still concerns about its risks, particularly whether it increases the likelihood of breast cancer. The lack of definite answers about HRT creates a tough decision for postmenopausal women and their doctors: Should they use it or not?

FINDING ANSWERS

To offer guidance to women and their doctors, the National Heart, Lung, and Blood Institute (NHLBI) and other units of the National Institutes of Health (NIH) started a major clinical trial in 1987—the "Postmenopausal Estrogen/Progestin Interventions Trial," known as PEPI.



Study Helps Women Decide About HRT

PEPI's other sponsors are the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute on Aging.

PEPI was conducted at seven clinical centers across the United States and followed 875 women for 3 years. At the

start of the trial, the women were ages 45-64. All were healthy and postmenopausal; about a third had had a hysterectomy (removal of the uterus). Participants were of various races but mostly white. All were closely monitored.

PEPI's main goal was to see what effects different regimens of estrogen alone or in combination with progestin or a placebo would have on key risk factors for heart disease, such as increased cholesterol and high blood pressure. (A placebo looks like a drug but has no biological effect.) It also was not clear whether a progestin would reduce or enhance estrogen's positive effects on cardiovascular health, and if it would protect the uterus from bad effects.

PEPI also examined HRT's effects on bone mass (mineral density) and quality of life. Decrease in bone mass is called osteoporosis, a severe thinning of the bones that can cause fractures, a serious problem for older women. About 20 percent of women over age 50 are at risk of developing osteoporosis.

Additionally, PEPI compared the effects of cyclic and continuous use of progestin. Cyclic use means taking a medication for only some days of each month, while continuous use means taking the drug daily throughout the month. These use options are important for women who may want to use HRT but not have the bleeding problems that can result from the cyclic use of progestin.

PEPI tested four hormone regimens: estrogen alone, taken daily; estrogen taken daily and a synthetic progestin, MPA (medroxyprogesterone acetate), taken 12 days a month; estrogen and MPA taken daily; and estrogen taken daily plus micronized progesterone (a natural progesterone), taken 12 days a month.

Results for heart disease risk factors, endometrial cancer risk, and bone mass are given below; other results are still being analyzed and have not yet been published.

HEART DISEASE RISK FACTORS

PEPI found that each of the active hormone therapies improved key heart disease risk factors:

- All hormone regimens raised levels of high-density lipoprotein (HDL), also called the “good cholesterol” because it helps remove cholesterol from the bloodstream.
- All hormone regimens decreased about equally the levels of low-density lipoprotein (LDL), termed the “bad cholesterol” because it carries most cholesterol and fat through blood vessels, where they can build up.
- No hormone regimen increased blood pressure or caused weight gain.
- All active regimens lowered fibrinogen levels. Fibrinogen allows blood to clot more readily, increasing the risk of heart disease and stroke.

ENDOMETRIAL (UTERINE LINING) CHANGES

All three estrogen plus progestin therapies prevented overgrowth of the uterine lining, which is called hyperplasia.

Women with a uterus who took estrogen alone had a higher risk of hyperplasia.

BONE DENSITY

PEPI found that HRT not only slows the bone loss that occurs with menopause, but also significantly increases bone mass. These effects on bone were strongest among older women and those who had not recently used hormones. All of the hormone regimens increased bone density. Smokers, who generally lose bone mass more quickly than nonsmokers, gained as much bone mass on average as nonsmokers.

DECIDING ON HRT

PEPI cannot answer every question about HRT. For instance, the trial was not large enough and did not last long enough to examine breast cancer issues. However, other research suggests HRT slightly increases that risk and perhaps only in women who take it for 5 or more years.

PEPI will release findings in the future about HRT's effects on quality of life. But more research is needed to provide women with more definitive guidelines about HRT. Questions remain about when to start and how long to continue HRT, the minimum dose of progestin needed to prevent hyperplasia, and differences in effects among estrogens and progestins, and from various regimens. Studies under way at NIH and elsewhere are trying to find more answers. (See next two stories, for more information on HRT and research). •

Louise Williams, writer/editor, National Heart, Lung, and Blood Institute.

How to Decide

To decide whether or not to use HRT, a woman should talk with her health care provider about her risk of heart disease, osteoporosis, and cancer, her family medical history, and quality of life issues of importance to her.

These guidelines may help in selecting a type of HRT:

- Postmenopausal women who have not had a hysterectomy should consider taking a therapy that combines estrogen with progestin or natural progesterone. A woman with a uterus who decides to take estrogen alone should have a yearly endometrial biopsy (examination of the uterine lining).
- Postmenopausal women who have had a hysterectomy get no added cardiovascular or bone-mass benefit from adding a progestin. These women are not at risk for endometrial hyperplasia, and they can use estrogen alone.

Finally, women who use HRT should periodically review their status with their doctor. They also should be alert for signs of trouble, particularly abnormal bleeding, dizziness, or severe headaches, and immediately report these to the doctor. They may or may not be due to the HRT.

TALKING WITH YOUR DOCTOR ABOUT HRT

If a woman is considering HRT, she should talk to her doctor about whether HRT is right for her. It is important to ask questions and express concerns. Here are some sample questions:

- Should I take hormones? Why?
- How could hormone therapy improve my heart disease risk factor profile?
- At what age should I begin?
- What is the best regimen for me? Why?
- How long should I stay on the therapy?
- If breast cancer has occurred in my family, should I consider HRT?
- If I have had breast cancer, should I consider HRT?
- What follow-up tests will I need? How often will I need to take each test?

Check in with your doctor on a regular basis to review your health status and your risk profile, which may change over time.

Do?

What's a Woman to Women's Health Initiative Will Provide Needed Data

A 53-year-old woman sits down in her physician's office. "Doctor, I haven't been feeling like myself for quite some time now, ever since I went through menopause," she says. "I've been hearing a lot about estrogen supplements and hormone therapies. Some of my friends are taking them and they feel great. They say it prevents heart disease and osteoporosis. Other women I know say they want nothing to do with them. They say they have had side effects and may cause cancer. Should I be taking these? Will they help me feel more like my old self? How serious are the side effects? What should I do?"

Women past menopause are finding that these are some of the toughest questions to deal with when trying to decide whether to supplement the hormones no longer naturally produced by their bodies. Hormone replacement therapy (HRT) for postmenopausal women has long been the subject of much debate. Of the numerous large studies conducted to date, none has been able to resolve the difficult questions for which these women and their physicians seek definitive answers.

Adult women over the age of 50 represent 14 percent of the American population, or 37.5 million people, according to the 1990 United States census. With

the average life span of both men and women increasing and with the aging "baby boomer" population, postmenopausal women not only are growing in numbers but also now live one third of their lives after the average age of natural menopause at 51.

SHORT-TERM USE RELIEVES SYMPTOMS

About 75 percent of all women experience some adverse symptoms surrounding menopause. These symptoms are believed to be caused by the loss of the hormone estrogen and its beneficial effects. While these symptoms can vary in intensity among different women, the brain, bones, heart, blood vessels, vagina and skin are typically affected at or after menopause. A woman may experience hot flashes, depression, sleep disturbances, inability to concentrate, and memory lapses. A decrease in bone density can increase the potential for fractures, and coronary heart disease may occur as a result of arteriosclerosis (hardening of the arteries). The cells in the lining of the vagina will diminish in their capacity to function causing the organ to become dry, which can result in painful intercourse. The skin will become thinner, wrinkled, and dry, and bruising and slower healing may be evident.

Estrogens are often prescribed for

women on a short-term basis to treat the symptoms of menopause for their duration, typically from several months to a year or two. While some women may have adverse reactions because they are more sensitive to supplemental estrogen than most, the majority will benefit with minimal or no risk from short-term estrogen supplements if the symptoms of menopause are troublesome for them. Research has shown that in women who still have their uterus, estrogen given alone can increase the risk of endometrial (lining of the uterus) cancer. Estrogen given with progestin to these women prevents this increase in risk.

The long-term use of HRT however remains controversial. Past studies of women taking estrogen for long periods to treat menopausal symptoms led to the recognition that estrogen supplementation can help prevent bone loss in postmenopausal women and thus reduce the risk of osteoporosis. However, the long-term effects on women of taking supplemental estrogen for many years, even decades, is only beginning to be understood. Some recent observational studies have indicated that HRT may have a role in preventing heart disease in these women, while other research may suggest an increased risk of breast cancer in women taking supplemental hormones.



Prior to menopause the rates of heart disease in women are low, and they seem to be protected against the development of cardiovascular disease. However, after menopause the risk of heart disease in women rises dramatically and becomes the leading cause of death in women. This observation suggests that female hormones *may* exert a protective effect, reducing cardiovascular risk.

PREVIOUS STUDIES SUGGEST BENEFITS

There are more than 40 studies in the medical literature concerning hormone replacement therapy and its effects upon the cardiovascular system. The weight of evidence from these studies does suggest that there is about a 50 percent reduction in cardiovascular disease for women who took hormone replacement compared to those who did not.

While hundreds of women have participated in these studies, they have had limitations. These studies have been observational studies, which cannot resolve questions about the risks and benefits of HRT. In observational studies, women who choose to take hormones are compared to those who choose not to take hormones. Women who choose to take hormones may be different from those who do not. For example, women who choose to take hormones tend to be healthier, less obese, more educated, less likely to smoke, more physically active, and have access to medical care. The differences in rates of heart disease seen between the groups may be due to those differences between the women rather than the fact they are taking hormones. Only in a clinical trial where women are randomly assigned to either take hormones or not to take hormones can any differences seen in disease rates be attributed strictly to HRT and not differ-

ences between the women electing to take a medication. Observational studies can give researchers clues, but randomized clinical trials give them the proof.

The Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial, a recent randomized double-blind clinical trial funded by the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH), showed estrogen to indeed be helpful in reducing certain risk factors associated with heart disease. (See previous story). However, the study did not look at actual disease *outcomes*, such as how many women developed heart disease or suffered strokes.

A woman's decision of whether to start HRT is further clouded by the many contradictory reports in the medical literature regarding the relationship between HRT and a potential increase in breast cancer. In June 1995 in the *New England Journal of Medicine*, the Harvard Nurses Health Study, a long-term observational study, reported a potential increased risk of breast cancer in women on HRT. That same summer, the *Journal of the American Medical Association* published a report of a case control study (a type of observational study that compares those with the disease under study with those who do not have the disease) that showed no association between HRT and breast cancer for women on hormone replacement. A review of the myriad of studies on HRT and breast cancer reveals that the data are limited and not convincing enough to draw definitive conclusions.

WHI: PROVIDING DEFINITIVE ANSWERS

The Women's Health Initiative (WHI), funded by NIH, is the first randomized clinical trial to examine the relationship

between hormones and heart disease and breast cancer. Begun in 1991, the WHI is a 15-year study to investigate the major causes of illness and death in postmenopausal women between the ages of 50 and 79 years old. This study will involve 164,500 women, 64,500 of whom will be in the clinical trial. One of the major components of the WHI will be a hormone replacement therapy intervention that will look specifically at the effect of long-term HRT on coronary heart disease and secondarily its effects on fractures as a result of osteoporosis. Another component of the WHI will be an observational study, which will involve 100,000 women who will receive no specific intervention. These women will be followed over an extended period to discover predictors and biological markers for disease. Researchers hope that a comprehensive study like the WHI will provide the definitive answers women need to make an informed decision about HRT.

IN THE MEANTIME, WHAT'S A WOMEN TO DO?

The decision to start short-term HRT for the alleviation of menopausal symptoms is dependent on how troublesome the symptoms are for a woman. The benefits are clear and the risks are minimal. However, to make the long-term commitment to hormone replacement, a woman and her physician must discuss her risks for cardiovascular disease and osteoporosis. The potential *benefits* for the cardiovascular system and a reduced risk of osteoporosis must be weighed against the potential *risk* of breast cancer and endometrial cancer. In addition, the contraindications and precautions of estrogen replacement therapy, such

as unexplained vaginal bleeding, active liver disease, chronic impaired liver functions, or recent vascular thrombosis (blood clotting) need to be considered.

Treatments that lower the level of fats in the blood, high blood pressure medication, and low dose aspirin are important in the prevention and management of coronary heart disease. For

osteoporosis, alternative therapies may include calcium and vitamin D supplements, agents such as alendronate and calcitonin, and preventive therapies such as exercise and calcium-rich diets. Only with all the facts can a woman and her physician make an informed decision about what is best. Women who are interested in participating

in the WHI should call 1-800-54-WOMEN. •

Loretta P. Finnegan, M.D., director, Community Prevention and Outreach, Women's Health Initiative.

Vivian W. Pinn, M.D., director, NIH's Office of Research on Women's Health, and a WHI study co-chair.

Be A Part of The Answer

The National Institutes of Health (NIH) is recruiting more than 164,500 women of various socioeconomic and ethnic backgrounds to participate in the Women's Health Initiative (WHI), a \$628 million, 15-year project that is one of the most definitive, far-reaching clinical trials of women's health ever undertaken in the United States.

The study will examine how diet, hormone therapy, and calcium and vitamin D might prevent heart disease, breast and colorectal cancer, and osteoporosis. These chronic diseases are the major causes of death, disability, and frailty in older women.

A woman may be eligible to participate in the WHI if she is:

- 50-79 years old
- past menopause or the "change of life"
- planning to live in the same area for at least 3 years

Women interested in participating in the WHI can call 1-800-54-WOMEN to be connected to a WHI clinical center in their area.

WHI CENTERS

ALABAMA:

University of Alabama at Birmingham, Birmingham

ARIZONA:

Arizona Disease Prevention Center, Tucson

CALIFORNIA:

Harbor-UCLA Research and Education Institute, Torrance
Kaiser Permanente Foundation Research Institute, Oakland
UCLA School of Medicine, Los Angeles
University of California at San Diego, La Jolla
University of California Irvine Medical Center, Orange
University of California at Davis, Sacramento
Stanford University, Palo Alto

FLORIDA:

University of Miami School of Medicine, Miami
University of Florida College of Medicine, Gainesville

GEORGIA:

Atlanta Vanguard Clinical Center, Decatur

HAWAII:

University of Hawaii, Honolulu

ILLINOIS:

Rush Presbyterian-St. Luke's Medical Center, Chicago
Northwestern University, Chicago

IOWA:

University of Iowa College of Medicine, Iowa City

MASSACHUSETTS:

Brigham and Women's Hospital, Boston
University of Massachusetts Medical School, Worcester

MICHIGAN:

Wayne State University/Hutzel Hospital, Detroit

MINNESOTA:

Shapiro Center, Minneapolis

NEVADA:

University of Nevada School of Medicine, Reno

NEW JERSEY:

University of Medicine and Dentistry of New Jersey, Newark

NEW YORK:

State University of NY at Stony Brook, Stony Brook
Albert Einstein College of Medicine of Yeshiva University, Bronx
State University of New York at Buffalo, Buffalo

NORTH CAROLINA:

Bowman Gray School of Medicine, Winston-Salem
University of North Carolina at Chapel Hill, Chapel Hill

OHIO:

Ohio State University, Columbus
University of Cincinnati Medical Center, Cincinnati

OREGON:

Kaiser Permanente, Portland

PENNSYLVANIA:

University of Pittsburgh, Pittsburgh

RHODE ISLAND:

The Memorial Hospital of Rhode Island, Pawtucket

TENNESSEE:

University of Tennessee, Memphis

TEXAS:

Baylor College of Medicine, Houston
The University of Texas Health Science Center at San Antonio, San Antonio

WASHINGTON, DC:

Medlantic Research Institute, Washington
The George Washington University, Washington

WASHINGTON:

Fred Hutchinson Cancer Research Center, Seattle

WISCONSIN:

University of Wisconsin, Madison
Medical College of Wisconsin, Milwaukee



NIA: Paving the Way for Better Decisions about Hormone Replacement

NUMEROUS STUDIES
PROVIDE BETTER
UNDERSTANDING
OF MENOPAUSE

It's hard to find a middle-aged woman who isn't confused, or at least concerned, about how she'll handle menopause when the time comes. On one hand, women are told that taking hormone replacement therapy (HRT) will relieve symptoms—hot flashes, bones made brittle by osteoporosis, and even heart disease. On the other hand, women are afraid that the same HRT that relieves symptoms may also increase their risk of breast and uterine cancer, or blood clots, which can lead to strokes and heart attacks.



There's no simple formula for whether or not a woman should take HRT after menopause. It's a decision each woman must make, with her physician, based on her health history, risk factors, and personal values. (See previous story on PEPI). With 1.3 million women reaching menopause in the United States each year, and the number growing as the baby-boom generation ages, the National Institute on Aging (NIA), part of the National Institutes of Health (NIH), has increased its commitment to further establishing the risks and benefits of HRT.

NIA's search for answers is an important one because the diseases and disabilities that can result from menopause exact not only a personal toll on women, but also a financial toll on society. By the year 2000, an estimated 70 million U.S. women will be postmenopausal, putting them at risk of osteoporosis and of heart disease, the number-one killer of women in the United States.

Menopause occurs when women's ovaries reduce the amount of estrogen they make, usually around the age of 50. The dramatic drop in this reproductive hormone causes widespread

changes; in fact, NIA scientists are finding that estrogen affects more tissues and organs than "anyone could have ever imagined," says Tamara Harris, M.D., of the NIA Geriatric Epidemiology Office. HRT replaces the estrogen formerly secreted by the ovaries (the hormone progestin is added to HRT to help prevent uterine cancer, since estrogen therapy may increase the risk).

FINDINGS: PROS AND CONS

One of NIA's most exciting recent findings involves estrogen's apparent effect on the brain; specifically, on Alzheimer's disease. In two independent studies, researchers found that postmenopausal women taking HRT were significantly less likely to develop Alzheimer's than were women who had never taken HRT. "These data are very preliminary, but they do suggest that it may be possible to treat or delay Alzheimer's disease," says Neil Buckholtz, Ph.D., Acting Associate Director of the NIA Neuroscience and Neuropsychology of Aging Program. One of the studies evaluated patients in the NIA Baltimore Longitudinal Study on Aging; the other also was funded by NIA.

INVESTIGATORS THEORIZE
THAT HIGH BMD SCORES
SHOW THAT A WOMAN'S
BONES HAVE BEEN PROTECTED
BY HIGH LEVELS OF HER
BODY'S OWN ESTROGEN
OVER HER LIFETIME.

Other findings are less positive. Some, but not all, studies suggest that risk of breast cancer increases with use of HRT. Investigators funded in part by NIA now have early evidence suggesting that bone mineral density (BMD), a test traditionally used to predict the likelihood of developing osteoporosis, may also identify which older women are at higher risk of breast cancer. Older women with BMD in the higher range—in other words, women less likely to develop osteoporosis—appear to be up to two-and-a-half times more likely to develop breast cancer as are women with lower BMD scores (it's worth noting, however, that most older women don't have high BMD).

Investigators theorize that high BMD scores show that a woman's bones have been protected by high levels of her body's own estrogen over her lifetime. It may be that the same high lifetime estrogen levels that cause high BMD scores also put women at greater risk of breast cancer. The study raises the question of whether HRT by itself also increases a woman's risk, and underscores the need for women to take their health histories—including family history of breast cancer—into account when considering HRT. It also suggests a potential new role for BMD in making decisions about hormone replacement.

Assessing risks is important, but it's just as important to assess the benefits of HRT when considering whether or not to take it. For example, HRT has been shown to help protect postmenopausal women from osteoporosis and heart disease. The potentially devastating effects of these diseases shouldn't be minimized. Broken spines and hips are among the more dangerous consequences of osteoporosis, and they often begin a deadly cycle that robs older women of their independence and their health. Prolonged bedrest leads to more disability, leading to more inactivity, leading to more disability, and so on.

Each year, almost 300,000 hip fractures occur in the United States alone, at an estimated cost of \$7–10 billion in medical and nursing services. The death rate of patients with a broken hip is 12 to 20 percent higher than that of other people in the same age group. A recently completed clinical trial revealed that BMD decreased in the spines and hips of postmenopausal women not taking HRT, putting them at risk of osteoporosis in those bones, but increased in those who took HRT, reducing their risk of osteoporosis. NIA joined other NIH institutes in supporting this far-reaching study of the effects of estrogen replacement.

The same study confirmed another of HRT's protective effects. It appears to play a role in reducing unfavorable

More Findings on Menopause from NIA

WHAT WE NOW KNOW

Results from previous studies suggest that:

- HRT loses its effectiveness against bone loss in women older than 75, underscoring the need for alternative strategies.
- For optimal protection against fractures, estrogen should be initiated soon after menopause and continued indefinitely.
- HRT doesn't cause the weight gain many women experience in their later years.
- Overall, HRT use among older women is low, despite its potential to protect them against heart disease and osteoporosis. The main reason women 65 and older don't start HRT is their fear that it's harmful.
- A woman's total number of reproductive years is a better predictor of her risk of osteoporosis than is her age at menopause.
- Estrogen levels increase in the years before menopause. This finding may explain why many women suffer gynecological problems, including heavy bleeding, before menopause.
- HRT blocks some of the potentially harmful changes in cholesterol levels that blood-pressure-lowering drugs called thiazide diuretics can cause.
- A combination of exercise and HRT improves cholesterol levels more than either exercise or HRT alone.
- In women 65 or older, HRT doesn't improve muscle strength or neuromuscular function, and doesn't reduce the risk of falling.
- Hot flashes follow a predictable pattern over 24 hours, and are triggered by an increase in body temperature. The higher temperature may cause the sleep disturbances some women experience during menopause.
- Paced respiration, a behavioral technique that involves slow, deep abdominal breathing, can reduce the frequency of hot flashes.
- In early menopause, HRT keeps the kidneys from excreting as much calcium as usual. Estrogen reduces the amount of calcium bones lose, leading to increased levels of parathyroid hormone, which in turn cause the kidneys to reabsorb calcium rather than eliminate it as waste. Adequate calcium levels are important for bone strength.
- Perimenopause—the interval surrounding and including menopause—has begun when women have a gap of three to 11 months between menstrual periods, or when women who don't skip menstrual periods before menopause experience increasing menstrual irregularity. Before investigators in the NIA-funded Massachusetts Women's Health Study established this definition by studying menstrual patterns in 1,550 women, research into such issues as whether HRT should be started during perimenopause was hampered by lack of a standard classification. •

levels of cholesterol and fibrinogen. Fibrinogen is necessary for normal blood clotting, but is also a factor in some heart attacks.

NIA will release findings from its recently completed Sites Testing Osteoporosis Prevention/Intervention Treatments (STOP/IT) study. STOP/IT investigators examined the effects of HRT, alone and combined with calcitriol (the active form of vitamin D), compared to other therapies, including weight-bearing hip exercises and supplements of calcium combined with vitamin D.

SEVERAL INSTITUTES AT NIH, AND NIA IN PARTICULAR, ARE NOW FOCUSING ON THE BIOLOGY AND PHYSIOLOGY OF THE MENOPAUSAL TRANSITION—ON HOW MENOPAUSE-ASSOCIATED CHANGES LIKE OSTEOPOROSIS, CARDIOVASCULAR DISEASE, HEAVY BLEEDING, AND HOT FLASHES DEVELOP IN THE FIRST PLACE.

“The STOP/IT study will give us a better sense of what the most effective interventions against osteoporosis are likely to be for women and men over 65 years of age,” says Sherry Sherman, Ph.D., of the NIA Geriatrics Program.

Among the reasons the STOP/IT study is important is that it focuses on women and men 65 and older, and on how different osteoporosis treatments and preventive measures affect hip-bone density. Most studies have focused on the bones of the spine rather than the hip in younger women 50 to 60 years old.

The sidebar entitled “More Findings from NIA” highlights results of some other recent menopause and HRT studies.

NEW DIRECTIONS

In the past, research has focused on treatments for post-menopausal health problems. Heightened interest in women’s health research has led to a paradigm shift. Several institutes at NIH, and NIA in particular, are now focusing on the biology and physiology of the menopausal transition—on how menopause-associated changes like osteoporosis, cardiovascular disease, heavy bleeding, and hot flashes develop in the first place.

“We expect our research to result in better measures, pharmacologic and nonpharmacologic, for preventing or reducing the severity of menopause-related symptoms,” says Francis L. Bellino, Ph.D., of the NIA Biology of Aging Program. Among the many nonpharmacologic approaches under consideration are exercise and consumption of plant compounds called phytoestrogens.

In 1994, NIH launched a longitudinal study of midlife health, including menopause, called the Study of Women’s Health Across the Nation (SWAN).^{*} Investigators are evaluating physical, psychological, and social changes in women who don’t take HRT as they reach menopause and the years after. Over 5 years, researchers at the 7 sites comprising SWAN will study 3,200 women, taking into account biological factors, lifestyle, health status, ethnicity, and other elements.

Learning about the biological processes of menopause and determining factors that influence those processes is just one of the SWAN researchers’ goals. Another is to document normal biological and psychosocial aspects of midlife in women from ethnic groups in whom menopause has not been studied extensively. The researchers also want to establish a clearer

Current NIA Research on Menopause and Hormone Replacement

WHAT WE WANT TO KNOW

Ongoing studies are looking at the following areas:

- A recent NIA study suggests that HRT may reduce the risk of developing Alzheimer’s disease. Researchers are now evaluating whether or not HRT will delay progression or relieve symptoms in women who already have the disease. Another study is focusing on the effects of HRT on cognition in men and women.
- A combination of estrogen and human growth hormone is included in a 5-year NIA-funded study of trophic factors—hormones that promote growth. Researchers want to know if replacing trophic factors as their levels decrease with age will prevent frailty and disability, major causes of loss of independence in older people.
- Researchers are conducting tests to find out if estrogen combined with low doses of parathyroid hormone, which have been shown to stimulate bone formation, will strengthen bone in women who have osteoporosis.
- Other researchers are comparing different combinations of estrogen and bone-strengthening drugs called bisphosphonates.
- Adding progestin to estrogen therapy is beneficial in terms of protection against uterine cancer. But, like any hormone, progestin can have side effects, and moodiness is one of them for some women. A 5-year NIA-funded study is evaluating not only the effects of progestin on bone, but also its effects on mood and cognition.
- Researchers are comparing different modes of administration of estrogen, including an injectable microcapsule. Taken orally, estrogen must pass through the liver, but as an injection, it reaches its targets more directly. •

definition of the “perimenopause”—the interval surrounding menopause—and to find out more about what role the perimenopause plays in gynecologic problems that midlife women tend to develop.

To ensure that SWAN is sensitive to ethnic differences, researchers have conducted focus groups of the populations included in the study—African-American, Caucasian, Chinese, Hispanic, and Japanese women. As a result, questionnaires used by study participants include cultural variations appropriate for each population.

At the NIA Gerontology Research Center in Baltimore, Maryland, 100 African-American women and 100 Caucasian

^{*} SWAN is funded by NIA, which awarded the initial grants, and by the National Institute of Nursing Research, the National Institute of Child Health and Human Development, and the National Institute of Mental Health. Other funding comes from the NIH Office of Research on Women’s Health, the Office of Alternative Medicine, and the Office of Behavioral and Social Sciences Research. The Fetzer Institute in Kalamazoo, Michigan, is also providing funding.



women are being recruited for a study of the perimenopause as part of the Baltimore Longitudinal Study on Aging (BLSA). These volunteers return to the BLSA's center every 3 months for a review of their symptoms and for measurement of reproductive hormones, growth hormone, and body composition. Every 6 months, the volunteers' BMD is measured. The data gleaned from this study will add to researchers' understanding of menopause, and may help to establish the appropriate timing for starting HRT and to identify traits that predict whether or not a woman should take HRT.

See "Current NIA Research on Menopause and Hormone Replacement" for highlights of other ongoing studies.

GETTING THE WORD OUT

Research findings on menopause and HRT are helpful only to the extent that women and health practitioners know about them. Among other projects, NIA grants have resulted in "What's New with Menopause," coproduced with the NOVA television series; videotapes and booklets; and "Menopause: Myths & Realities," a booklet based on the findings of the Massachusetts Women's Health Study. The NIA Public Information Office also provides free literature and information on menopause and HRT.

Often, women whose risk factors for heart disease and osteoporosis make them good candidates for HRT choose not to

take it. NIA-funded researchers have studied why women make the decisions they do. Through extensive interviewing and focus groups, a recently completed study revealed that women tend to base their decisions about HRT as much on personal values as on biomedical issues.

"We found that values are far more influential than originally thought," says Dr. Thomas R. Taylor, of the University of Washington. He and his colleagues also found that physicians are almost uniformly in favor of recommending HRT, but that women tend to base their decisions more strongly on factors other than their doctors' recommendations. Dr. Taylor's group plans to follow up on these findings by establishing a world-wide web site on the internet that will help women sort out information about HRT.

As the NIA studies generate more results in the years to come, the amount of useful information women will have to help them make decisions about HRT is sure to grow. •

Susan Cahill, writer/editor, National Institute on Aging.

Free literature about menopause and hormone replacement therapy may be obtained from the National Institute on Aging by calling 1-800-222-2225.

NCI STUDY WILL ANSWER QUESTIONS REGARDING MANAGEMENT OF CERVICAL LESIONS

YOU VISITED YOUR GYNECOLOGIST A FEW DAYS
AGO FOR YOUR ANNUAL PAP SMEAR, THE
ROUTINE TEST USED FOR DETECTING CERVICAL
CANCER, AND NOW YOU ARE CONGRATULATING
YOURSELF ON THE PREMISE THAT NO NEWS IS
GOOD NEWS, WHEN SUDDENLY THE PHONE
RINGS AND ON THE OTHER END IS YOUR
GYNECOLOGIST. THE LABORATORY HAS REPORTED
THAT YOUR PAP SMEAR SHOWS A MILD
ABNORMALITY IN CELLS LINING THE CERVIX.
RELIEVED THAT IT IS NOT CANCER, YOU ASK YOUR
DOCTOR, "HOW DO WE TAKE CARE OF IT?" AN
EASILY ANSWERED QUESTION, RIGHT? WRONG.

Unfortunately, for many gynecologists it is a hard-to-answer, controversial question. However, a newly launched National Cancer Institute (NCI) study will address this question and hopefully provide answers for the 2 to 3 million women each year who learn that their latest Pap smear shows a mild abnormality.

These mild abnormalities, known as ASCUS (atypical squamous cells of undetermined significance) and LSIL (low-grade squamous intraepithelial lesions), are often evaluated with colposcopy, an invasive procedure that involves studying the cervix under magnification and taking biopsies of any abnormal tissue. In many cases the mildly changed cells will revert to normal without treatment. So, are we doing too much by performing colposcopy and taking biopsies of tissue immediately? Are there better and less invasive ways of managing these abnormalities?

WOMEN MAY BE OVERTREATED

The answer to both questions may be yes, and according to Diane Solomon, M.D., one of the study's principal researchers, "we may be overtreating these mild abnormalities in many cases." To explore this theory further, NCI will enroll 7,200 women diagnosed with mild abnormalities to "determine whether physicians can safely take an approach that is less aggressive," adds Solomon. "If so, then millions of women could avoid colposcopy and biopsy each year."

In 1997, it is estimated that in the United States 14,500 cases of cervical cancer will be diagnosed and 4,800 cervical cancer deaths will occur. Of the

OPINIONS DIFFER ON TREATING LESS SERIOUS ABNORMALITIES

approximately 50 million Pap tests that will be performed, 4 percent to 8 percent will show mild abnormalities. It is estimated that 2 million cases of ASCUS and 1.25 million cases of LSIL will be discovered as well as 300,000 cases of a more severe abnormality known as HSIL (high-grade squamous intraepithelial lesion).

Since HSIL has a much higher chance of developing into cancer, there has been little controversy about how to treat it. Aggressive treatment with immediate colposcopy and biopsy of abnormal tissue is the agreed upon method of handling this type of lesion. But disagreement remains about how to treat the mild lesions.

STUDY WILL LOOK AT ALTERNATIVES TO TREATMENT

The NCI-sponsored ALTS (ASCUS/LSIL Triage Study) trial, which will complete enrollment in 1998, will look at three ways to manage these mild abnormalities:

1. Immediate Colposcopy—an aggressive management option during which a physician examines the cervix under magnification and biopsies any abnormal tissue for further study. This approach is often used by physicians in the United States because a mild abnormality, such as ASCUS or LSIL, may, in a small portion of cases, indicate the presence of HSIL or risk of developing it.

2. Conservative Management—repeating the Pap test every six months because most mild abnormalities return to normal without treatment. This is the method of follow up most commonly used in Canada and Europe.

3. HPV Triage—testing for certain types of human papillomavirus (HPV) to determine which abnormalities need to be treated with immediate colposcopy and which can be followed through conservative management.

Another issue that gynecologists and other physicians agree upon is that HPV causes cervical cancer. According to NCI's Mark Schiffman, M.D., a co-principal investigator, most true abnormalities found via a Pap test are

directly linked to HPV infection. One of two major hypotheses that the study will examine is whether HPV testing can help in managing these mild abnormalities by using HPV test results to predict who is at higher risk of developing HSIL and needs to undergo colposcopy.

The other major hypothesis to be tested is that monitoring a patient who has ASCUS or LSIL with Pap tests every six months is a safe and effective way to manage these mild abnormalities. Additionally, ALTS will look at several other issues including: how immune-system factors may influence the course of HPV infections; how levels of folate (an essential vitamin) are related to cervical lesions; how the three man-

agement options compare cost-wise; how acceptable the options are to women and the ways in which the different options have affected their lives; and how to best recruit and retain minority women.

FOLLOW-UP ENSURES PATIENT SAFETY

The study, which will follow participants for three years, also has several built-in safety mechanisms so that no serious precancerous or cancerous lesions are missed. As each woman enters the study, she will have a cervigram, a magnified picture of the cervix, which will be examined by certified evaluators. This will be repeated at each



Dr. Diane Solomon

FACT REMAINS THAT MANY YOUNGER WOMEN WHO ARE AT HIGH RISK FOR HPV INFECTION AND OLDER WOMEN WHO ARE AT AN INCREASED RISK FOR DEVELOPING CANCER SIMPLY DO NOT HAVE REGULAR PAP TESTS.

follow-up visit and any patient whose cervigram shows suspicious looking tissue will undergo colposcopy. Quality control groups will also examine the results of the three management options, and, finally, all participants will have colposcopy performed at the end of the trial to verify that no serious abnormalities have been overlooked.

Enrollment for ALTS is ongoing at four sites: the University of Alabama, Birmingham; the University of Washington, Seattle; the University of Oklahoma, Oklahoma City; and the Magee-Womens Hospital, Pittsburgh.

Although data collected at the four ALTS centers will help answer a serious treatment question about how to manage the common mild abnormalities, ASCUS and LSIL, the fact remains that many younger women who are at high risk for HPV infection and older women who are at an increased risk for developing cancer simply do not have regular Pap tests. Furthermore, world-wide cancer statistics show that in areas where Pap tests are not widely available, cervical cancer is a leading cause of cancer death among women. "This [lack of screening] is a serious problem," says Solomon, "because regular Pap tests and treatment of precursor lesions are the key to preventing cervical cancer." •

Catherine Law, science writer, Technology Transfer Fellow, Office of Science Policy, National Cancer Institute.

HPV and Cervical Cancer

Infection with the human papillomavirus (HPV), which is mainly transmitted sexually, is directly connected to the development of cervical cancer. As with any sexually transmitted infection, having multiple partners puts a woman at higher risk for contracting the virus and thus developing abnormalities that can lead to cancer. However, few people understand what HPV is. The following questions should help you understand what HPV is and why it is connected to cervical cancer.

1. *What is human papillomavirus (HPV)?* HPV is actually a group of viruses with at least 70 different types. At least 30 of these types infect the cervix, and about 15 of these have been connected with cervical cancer. The cancer-associated types of HPV are called high-risk types. Both high-risk and low-risk types can cause abnormalities in the cervix, but it appears that abnormalities associated with high-risk HPV viruses turn more often into high-grade lesions or cancer. HPV-16 is the type most commonly found in precancerous and cancerous lesions, followed by HPV-18. In fact HPV-16 and 18, along with 11 other virus types, are responsible for 90 percent of HPV infections that result in HSIL, severe changes in cells lining the cervix, and cervical cancer.

2. *Who is at risk for HPV infection?* HPV infection is more common in younger age groups, particularly among women who are in their teens and late 20s. Because HPV is mainly spread through sexual contact, the greater the number of sexual partners the greater the risk. Women who became sexually active early, who have multiple sexual partners, and whose sexual partners have other partners are at increased risk. Nonsexual transmission is also possible. The virus often disappears, but viral DNA can be detected in cervical cells for years after infection.

3. *Does HPV cause cervical cancer?* Yes. Scientists have concluded that there is a causal relationship between HPV and cervical cancer. Scientists continue to study other factors that may also be required for the development of cancer, such as changes in the immune system.

4. *Does infection with a cancer-associated type of HPV always lead to a precancerous condition or cancer?* No. Most infections appear to go away on their own without causing any kind of abnormality. However, infection with cancer-associated HPV types may increase the risk that mild abnormalities, such as ASCUS (atypical squamous cells of undetermined significance) and LSIL (low-grade squamous intraepithelial lesions), will progress to more severe abnormalities, such as HSIL, or cervical cancer. With regular follow-up care by trained clinicians, women with precancerous cervical abnormalities should not develop invasive cervical cancer.

5. *Do LSIL and HSIL ever develop in the absence of any HPV infection?* Yes, but rarely. The cells in a vast majority of low-grade and high-grade cervical lesions have detectable HPV DNA. Researchers think that less than 10 percent of all LSIL and HSIL have no HPV DNA present. •

For answers to additional questions concerning HPV, ALTS, and cervical or other cancers, contact the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER.

THE BATTLE TO RELIEVE PAIN

GOOD
NEWS
FOR
WOMEN



PAIN COSTS THE NATION
MORE THAN \$100 BILLION
ANNUALLY IN HEALTH CARE
AND LOST PRODUCTIVITY.
THIS CONDITION GENERATES
NEARLY 40 MILLION VISITS TO
HEALTH CARE PROVIDERS AND
CAN PROLONG HOSPITAL
STAYS, IMPEDE RECOVERY,
AND INTENSELY AFFECT
QUALITY OF LIFE. IT IS A
DANGEROUS, OFTEN
UNDERESTIMATED PROBLEM
THAT DESERVES INCREASED
RESEARCH ATTENTION.

In practical life, woman is judged by man's law, as if she were a man, not a woman," commented playwright Henrik Ibsen. Until recently, that was certainly true for much of clinical therapeutic research. Fortunately, scientific knowledge is increasing our understanding that women and men differ in their risk for type and severity of disease, and also in type, and effectiveness of treatments. Clinical trials have frequently tested new procedures and drug products only on men. The resulting therapies have then been applied to both sexes, even though little was known about effectiveness for women. This practice is changing as scientists contin-

ually uncover new information that gender is important. Now treatment for pain—a pervasive, sometimes perilous symptom—can be added to the list of health issues where a person's gender may make a difference.

Pain is highly subjective and for that reason difficult to study. The familiar expression "I feel your pain" indicates comforting empathy, not actual reality, because as far as is known no two people feel pain the same way. New evidence now indicates that, not surprisingly, pain relief also differs—but the difference is along male/female lines. Research supported by the National Institute of Nursing Research (NINR) has found that women obtain relief with fewer side effects from commercially available but not widely used painkillers known as kappa-opioids. Men, however, receive little benefit from the drug.

According to the study's Principal Investigator, Dr. Jon D. Levine, of the University of California, San Francisco, "We had been studying pain control mechanisms for several decades. Since pain is multidimensional, we believed the time was right to look at other factors, such as the influence of gender, ethnicity and age. We laboriously and exhaustively reviewed the published literature and we could not find a single study comparing the responses of men and women for any type of painkiller."

WOMEN FOUND TO HAVE GREATER PAIN RELIEF THAN MEN

The investigative team then set out to study the pain relief capabilities of kappa-opioid drugs, which were given to 28 young men and 20 young women who had their wisdom teeth removed—a procedure that typically produces

STUDIES HAVE TOLD US
WOMEN ARE MORE SENSITIVE
TO PAIN, BUT ONE INTRIGUING
STUDY INDICATES BOTH MEN
AND WOMEN BELIEVE
WOMEN ARE BETTER ABLE TO
COPE WITH PAIN.

moderate to severe pain. The findings surprised the scientists by showing a striking difference. Women experienced much greater and longer-lasting pain relief than men.

Dr. Christine Miaskowski, a co-investigator on the study, says that "One reason kappa-opioids are of interest to our research team is that they have been largely ignored as painkillers in clinical practice in favor of the more powerful mu-opioids, such as morphine, codeine, and percodan." Pharmaceutical company clinical testing, mainly on men, showed kappa-opioids lacked painkilling power. The drug, however, is already in use for labor pain, which adds evidence to its gender-specific analgesic effects. The mu drugs, however, have the disadvantage of sometimes producing undesirable side effects, such as nausea and disorientation. On the other hand, kappa-opioids, such as nalbuphine or butorphanol used in the study, have many fewer side effects, although sometimes general malaise has been reported. "What's critical in this study," says Dr. Levine, "is a high quality of pain relief. It is important to feel 'normal' again."

Dr. Karen Berkley, a neuroscientist at The Florida State University in Tallahas-

see, who wrote a commentary on the study, said, "What is perhaps most important about the demonstration of sex differences in kappa-opioid analgesia is that it has raised our consciousness as much as it has raised many important questions." The study lays the groundwork for further exploration of such issues as the influence of hormones—is kappa-opioid effectiveness helped by estrogen or blocked by testosterone? What are the neurological implications? Do women have more kappa receptors on certain nerve cells than men, thus enabling kappa-opioids to block pain better? Dr. Levine points out that "the way the brain regulates pain relief may differ between the sexes. This is critical information for the development of new therapies to benefit both men and women." Other studies have shown that men and women also differ in their perception of pain. Women appear to have lower thresholds and less tolerance.

Continuing their work in this area, the study team plans a dual-pronged approach. They are going back to the lab to study gender differences at the basic science level, while in a clinical setting they will examine the effectiveness of kappa-opioid drugs for women with a variety of conditions.

Dr. Miaskowski says a special research challenge will be to enlarge the number of people available for study. "Our recent research deals with acute pain, so the kappa-opioid drugs are used for a short period of time. Their efficacy may not be appropriate for longer term use, such as in the case of chronic illnesses." She also looks forward to expanding research to other dimensions of the pain experience, including cognition and behavior. "Studies have told us women are more sensitive to pain, but one intriguing study indicates both men and women believe women are better

able to cope with pain. This merits further inquiry. And research on how gender may influence pain treatment is another important element," she adds, "since studies of patients with cancer and AIDS pain indicate women more likely to be undertreated."

NURSING RESEARCH FOCUSES ON PAIN

Pain relief, of course, is important for both men and women. The effects of pain cost the nation more than \$100 billion annually in health care and lost productivity. Pain generates nearly 40 million visits to health care providers and can prolong hospital stays, impede recovery, and intensely affect quality of life. It is a dangerous, often underestimated problem that deserves increased research attention.

Since many of the nation's 2.2 million nurses are on the front line in dealing with patient pain, nursing research has long focused on this distressing condition and its treatment. Investigators have developed tools to rate levels of pain, which are invaluable for treating patients too young or too sick to say what they feel. This is particularly important for infants, who are often undertreated because caregivers cannot determine the presence of pain or its intensity in this group. Fortunately, preliminary research offers some important cues. Physical signs, such as a grimace or reduced body movements and difficulties in being consoled, can indicate pain and the need to treat. For young children who have had surgery, a "pain measurement scale" is now in use that consists of a series of photos of a young child's face experiencing five different thresholds of pain. The patient points to the photo that most reflects the pain level he is experiencing, which then helps the health care provider determine

New Pain Consortium Promises Unified Effort

Banding together to advance research on pain, 21 NIH institutes and offices have combined their strengths to form a new trans-NIH Pain Research Consortium. Because almost all diseases have an element of pain, interest in understanding the underlying mechanisms and finding improved treatments extends throughout NIH. By pooling scientific talent and information, the Consortium aims to make the most of the expertise and technological resources available within NIH.

News of the Pain Research Consortium first came last November when NIH Director Harold Varmus announced its formation in his keynote address at the annual meeting of the American Pain Society. The Consortium plans to stimulate collaborative initiatives in pain research, encourage information sharing, coordinate extramural and intramural research programs on pain, and promote strong relationships both within NIH and with extramural scientists and patients. Spearheading these efforts are directors of two NIH institutes with a long-standing interest in pain research—Dr. Harold Slavkin from the National Institute of Dental Research and Dr. Zach W. Hall from the National Institute of Neurological Disorders and Stroke—who were appointed co-chairs of the Pain Research Consortium.

This is an exciting time in pain

research. At the most fundamental level, advances in genetics, neuroscience, and pharmacology are providing new tools and ways of understanding the basic mechanisms of pain. At the same time, new techniques of brain imaging, new clinical studies, and advances in integrative biology that connect pain with endocrine and immunological processes offer insights that may directly translate into new treatments. The link between pain and behavior also is an important one, as is the influence of cultural factors on patients' reactions to pain.

The Pain Consortium will consider a number of points of view as it sets its research agenda, including the perspectives of alternative medicine and gender differences in response to pain. Gender is an increasingly important area, as recent studies show that biologically men and women may not obtain pain relief in the same way, perhaps because of differences in the hormonal environment.

Under the direction of Drs. Slavkin and Hall, planning is underway for several initiatives. A major conference on "New Directions in Pain Research" held in November 1997 brought together established pain researchers with those from other, related fields to stimulate new ideas. The Consortium also will sponsor an annual NIH pain research symposium to promote contact among the diverse com-

munities of NIH pain researchers, including those concerned with basic research, clinical science, and behavioral research. To coordinate extramural research, program officers from the involved NIH institutes will exchange information about research portfolios, sources of information, and opportunities for collaborative activities. A Pain Interest Group—nicknamed "PIG"—has been created at NIH, made up of intramural scientists and other NIH staff working in the field of pain research.

In a nation with an aging population, there is an increasing

challenge to reduce chronic and debilitating diseases. Chronic pain results in enormous cost to the individual and to society. Although much progress is being made in our understanding of the neuroscience of pain, pain remains one of our most challenging and important problems in research and health care. The formation of the trans-NIH Pain Research Consortium is a significant step in advancing the fight against pain. •

Jody Dove, public affairs specialist, National Institute of Dental Research.

MEMBERS OF THE NIH PAIN RESEARCH CONSORTIUM

National Cancer Institute
National Center for Research Resources
National Institute on Aging
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Institute on Drug Abuse
National Institute on Deafness and Other Communication Disorders
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treatment. The scale's ethnic specificity—the photos show white, African-American, or Hispanic children—has been shown to help young children of diverse populations more accurately identify their pain.

Currently, NINR is playing a significant role in a major NIH pain research initiative that funds studies ex-

amining the links between biology and behavior; the similarities and differences of the pain experience; and ways in which pain can best be managed for different populations, including the elderly and ethnic minority groups. •

Linda Cook, information officer, National Institute of Nursing Research.

This article, "Kappa-opioids Produce Significantly Greater Analgesia in Women than in Men," was published in the November 1996 issue of *Nature Medicine*. In addition to NINR, NIH's National Institute of Dental Research and the Kaiser Community Services Program provided support for the study.

HELPS

WOMEN reENTER

CAREERS

FEMALE SCIENTISTS

IN SCIENTIFIC

LOOK TO NIH FOR

RESEARCH

SUPPORT IN

BALANCING WORK

AND FAMILY

A n NIH program—developed by the Office of Research on Women's Health—is assisting fully trained scientists to reestablish their careers after taking time off for family responsibilities. Begun in 1992, the ORWH Reentry Program is part of a larger effort to increase the representation of women in research careers and in positions of academic and scientific leadership.

"We know that many women have commitments to children and other family responsibilities, such as caring for aging parents, that often interrupt their careers," explains Dr. Vivian Pinn, director of NIH's Office of Research on Women's Health. "We wanted to provide a mechanism that enables women scientists to reenter the workforce with the training and support they need to resume their research careers."

Although the program is open to both men and women, the majority (93 percent) of participants, not surprisingly, are female. Several studies have shown that female scientists who leave their field for even a few years find it very difficult to return.

Dr. Beverly Kingsley, an assistant professor and a 1993-95 reentry awardee from the University of Oklahoma College of Public Health, explains that without retraining, reentry into the competitive world of scientific research is problematic for women scientists who leave traditional careers for several years. "Even if you keep up with the knowledge base there are a number of obstacles to overcome," says Kingsley. "Others' perceptions of you change when you take an unconventional approach to your career, and [that] can take its toll. In addition to providing an opportunity for retraining and reentry,

NIH support provides credibility, which, often is an issue.”

Another issue is the underrepresentation of women at all levels of scientific research. In 1991, women in academic institutions accounted for only 22 percent of Ph.D. scientists in 4-year institutions and only 9 percent of full professors. Women are also less likely to be tenured: only 35 percent of women scientists are tenured compared with 59 percent of their male counterparts. These figures are even more noteworthy considering the following statistics from 1991: women earned 50 percent of all baccalaureate degrees in science, 55 percent of all master’s degrees in science, and, in 1992, 39 percent of all doctoral degrees.*

PROGRAM PROVIDES FINANCIAL AND OTHER ASSISTANCE

The program works by supporting reentering scientists who receive supplemental funding for up to three years to work on a pre-existing NIH grant or collaborative project. Program participants have either a doctoral or medical degree and have been away from their careers an average of 4.4 years, most citing child care as the main reason for their absence.

In addition to providing financial assistance, the program offers the support of a mentor, usually the principal investigator on the NIH grant. The primary purpose of the mentor in the reentry program is to bring the awardee “back into the research fold.” Dr. Bruce Johnson, head of the National Cancer Institute’s Lung Cancer Biology Section at NIH, currently acts as mentor to Dr. Patricia Cortazar, a physician-researcher who left the workforce for four years to care for her children. “The reentry program is supporting Dr. Cortazar as a 3-year NCI clinical fellow conducting research on experimental treatments for lung cancer patients,” explains Dr. Johnson. “The NCI fellowship combines direct patient care

with experience in clinical research and is designed to assist physicians, such as Dr. Cortazar, to develop expertise in medical oncology.”

To date, 35 scientists have participated in the program, which is currently supported by 17 NIH institutes and centers. Each individual’s reentry experience is unique, reflecting the background, needs, and interests of the participants.

“Not only did I want to get back to the university after staying home to care for several family members,” explains Dr. Kingsley. “I also wanted to make a shift from laboratory work to human toxicology and I knew, in order to achieve those goals, I needed additional experience beyond the post-doctoral level. Several mentors from the reentry program were instrumental in providing valuable assistance and advice in terms of career development. Reentering scientists have a much better chance of succeeding if they have an academic [and personal] support system.”

ASSESSMENT WORKSHOP FINDS PROGRAM EFFECTIVE

At a recent workshop held at NIH to assess the strengths and weaknesses of the reentry program, program participants said that they felt the ORWH Reentry Program was “very effective” in helping them make the transition to an active research career and that additional efforts should be made to expand reach scientists who are less familiar with NIH. Program visibility could be increased, as some suggested, by announcing the program at meetings, in publications, and on the Internet.

Dr. Barbara Glick, a senior medical anthropologist and former reentry awardee from the Multnomah County Health Department in Portland, Oregon, and the Oregon State Department of Health, expressed an almost unanimous theme when she noted that many participants, especially the younger scientists, felt the need to extend the program an additional year in order to accommo-

“WE WANTED TO PROVIDE A MECHANISM THAT ENABLE WOMEN SCIENTISTS TO REENTER THE WORKFORCE WITH THE TRAINING AND SUPPORT THEY NEED TO RESUME THEIR RESEARCH CAREERS.”

date a variety of needs among the participants. Referring to the different levels of experience among the reentry scientists, she added, “It might be appropriate to have different program options: one for scientists who have been active in science for a number of years and another for reentry scientists who are less experienced, particularly in obtaining research funding. The training needs of scientists right out of graduate school are very different from those of an experienced scientist who has obtained grant funding and managed projects.”

Regardless of how the reentry program will be shaped to meet the growing demand for more researchers, the philosophy behind it—to demonstrate NIH’s commitment to develop ways to bring qualified scientific researchers back to their careers—remains the same. As stated by Dr. Pinn at the conclusion of the reentry workshop, “A career in science and family responsibilities should not be incompatible in today’s society.” •

* The ORWH Reentry Program Assessment, ORWH, NIH.

Mary Sullivan, public affairs specialist, Office of the Director, Office of Communications, and editor, NIH News & Features magazine.

TOPICAL MICROBICIDES

NEEDED TO HELP PREVENT HIV INFECTION AND OTHER STDs

The United States is in the midst of a “hidden epidemic” of sexually transmitted diseases (STDs), according to a 1996 Institute of Medicine (IOM) study. Although chlamydial infection, gonorrhea and other STDs are among the most common diseases reported to the Centers for Disease Control and Prevention (CDC) each year, the IOM study found that public awareness and knowledge of STDs were dangerously low.

WOMEN BEAR BURDEN OF STDs

More than 14 million people in the United States get STDs each year and, at current rates, at least one person in four will contract an STD at some point in his or her life. Women bear the brunt of the STD burden. In addition to being biologically more susceptible to certain STD pathogens than men, women experience more asymptomatic STD infections than men and consequently suffer more frequent and more severe STD complications. For example, pelvic inflammatory disease (PID), perhaps the most serious STD complication, affects more than 1 million women in the United States each year, and cervical cancer caused by infection with human papillomavirus kills more than 4,000 women annually in this country.

The AIDS epidemic compounds the urgency of this problem. Between 1985 and 1995, AIDS cases among women in the United States increased threefold and AIDS is now the fourth leading cause of death among women ages 25-44 in this country. Worldwide, new HIV infections are increasing most rapidly among women, who contract the virus primarily through heterosexual contact.

Despite the disproportionate health risk that STDs pose for women, avoiding them often is more problematic for women than for men. Condoms provide good protection against HIV infection and other STDs when used consistently during sex. But, as Penny Hitchcock, D.V.M., of the National Institute of Allergy and Infectious Diseases (NIAID), explains, condom use ultimately requires the consent and cooperation of the male partner—women cannot always successfully negotiate their use. And abstinence, the only fail-safe measure against STD infection, is not always an option for women, since non-consensual sex is an all-too-common reality.

“Just as hormonal contraceptives dramatically enhanced the ability of women to avoid unwanted pregnancy, effective female-controlled barrier methods are urgently needed to enhance the

ability of women to avoid HIV and other sexually transmitted infections,” says Dr. Hitchcock, chief of NIAID’s Sexually Transmitted Diseases Branch.

Dr. Hitchcock and Zeda Rosenberg, Sc.D., of the NIAID Division of AIDS, oversee NIAID efforts to develop topical microbicides—virus- and bacteria-killing gels, foams, creams or films—that women can apply intravaginally before having sex to protect themselves from STD pathogens.

“The ideal microbicide,” says Dr. Hitchcock, “will be unnoticeable, so it can be used without the male partner’s knowledge, if necessary; fast acting against HIV and a broad range of other STD pathogens; inexpensive; and safe for use at least one to two times daily.” She adds that microbicides should be formulated both with and without contraceptive properties, so women’s reproductive decisions do not affect their risk for STD infection.

NIAID Director Anthony S. Fauci, M.D., notes that numerous studies have shown that people with STDs have an increased risk for HIV infection. Topical microbicides, therefore, should be designed to protect against HIV directly, by blocking transmission of HIV during sex, and indirectly, by preventing other STDs.

“Given the alarming rate of new HIV infections among women in the United States and abroad, the development of safe, effective, female-controlled topical microbicides is a global priority and a central focus of NIAID’s STD research program,” says Dr. Fauci. “Both men and women will benefit from these products,” he adds. “By killing sexually transmitted pathogens in women’s vaginal secretions in addition to those in semen, topical microbicides will prevent

GIVEN THE ALARMING RATE OF NEW HIV INFECTIONS AMONG WOMEN IN THE UNITED STATES AND ABOARD, THE DEVELOPMENT OF SAFE, EFFECTIVE, FEMALE-CONTROLLED TOPICAL MICROBICIDES IS A GLOBAL PRIORITY AND A CENTRAL FOCUS OF NIAID'S STD RESEARCH PROGRAM.

female-to-male as well as male-to-female transmission of HIV and STDs.”

VARIETY OF APPROACHES UNDER INVESTIGATION

NIAID funding for topical microbicide research has more than doubled in recent years, increasing from \$5.3 million in 1994 to \$12.2 million in 1996.

“This is a long-term commitment that we will pursue until we have a number of products evaluated and available,” Dr. Fauci says.

Central to NIAID's research efforts are multiyear projects at four U.S. institutions. These Topical Microbicide Program Projects address a variety of basic and clinical research questions. Scientists at the University of California, Los Angeles, for example, are investigating protegrins, naturally occurring protein fragments with antibiotic properties. In laboratory experiments, researchers assess the activity of various protegrin formulations against HIV and pathogens causing gonorrhea, chlamydial infection, syphilis, genital herpes, and trichomonas. These studies may lead to better ways to treat people with STDs.

A research team at the University of Cincinnati's Children's Hospital Medical Center studies the microbicidal potential of over-the-counter spermicides as well as newly developed products. They also are exploring the disease-causing mechanisms of herpes simplex virus, chlamydia bacteria, and HIV, to gain a better understanding of the properties that microbicides must possess to prevent infection with these pathogens.

At Pennsylvania State University's Hershey Medical Center, NIAID-supported scientists are developing a system to predict the safety and effec-

tiveness of microbicides in clinical trials. They have developed an animal model in which human vaginal tissue has been grafted onto mice. Ultimately, the scientists will use the model to determine if experimental topical microbicides can destroy STD pathogens without harming the vaginal tissue.

Scientists at the University of Pittsburgh are evaluating a number of synthetic and naturally occurring microbicides in laboratory and clinical studies. Researchers led by NIAID grantee Sharon L. Hillier, Ph.D., recently discovered a correlation between lactobacilli, a type of bacteria that can occur naturally in the vagina, and protection from gonorrhea, bacterial vaginosis, and HIV infection. Lactobacilli produce hydrogen peroxide and other microbe-killing compounds. Based on this finding, scientists developed a lactobacillus vaginal suppository that enables these “good bacteria” to grow in the vagina. Clinical trials are under way to determine whether use of these suppositories can reduce women's risk of gonorrhea and bacterial vaginosis.

“We're very excited about the lactobacillus study,” says Dr. Hitchcock. “Enhancing the normal vaginal flora would be a natural and safe way to prevent gonorrhea and bacterial vaginosis, both of which have been strongly implicated as risk factors for HIV infection. A recent study indicated that direct protection from HIV infection may be possible with this approach.”

In addition to the lactobacillus study, NIAID is sponsoring a clinical trial of another new microbicidal product at Memorial Hospital in Providence, Rhode Island, one of NIAID's HIV Vaccine Efficacy Trials Network (HIVNET) sites. Researchers led by

Kenneth Mayer, M.D., are evaluating the safety of an acid-buffer gel, a compound designed to maintain the vagina's mild acidity. Scientists believe this acidic environment is hostile for HIV and other sexually transmitted organisms.

“Semen is very alkaline,” explains Dr. Rosenberg, “and raises the pH in the vagina to levels that are more hospitable to HIV and other sexually transmitted pathogens. The acid-buffer gel, we hope, will counteract the alkalinity of the semen and keep the vaginal pH low enough to kill pathogenic microbes.” Depending on the results of this study, further studies are planned for sites in Asia and Africa.

NIAID also sponsors clinical studies of over-the-counter spermicides containing nonoxynol-9 (N-9). Investigations in Cameroon and at HIVNET sites in Kenya will determine whether a vaginal film or gel containing this compound affects the transmission of HIV or other microbes.

“Research suggests that over-the-counter spermicides may offer limited protection against gonorrhea and chlamydial infection, but we currently do not know whether they would prevent HIV infection,” says Dr. Rosenberg. N-9, which works by disrupting the cell membranes of sperm, may also disrupt the cell membranes of vaginal tissue, creating microscopic cracks and abrasions that might facilitate HIV's entry into the bloodstream. “Since these products are already widely used, we need to understand what role, if any, they play in the transmission of HIV and STDs.” •

John Bowersox, writer/editor, National Institute of Allergy and Infectious Diseases.

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THE GENDER GAP IN AUTOIMMUNE DISEASES:

LOOKING FOR ANSWERS

HORMONES AND THE IMMUNE SYSTEM

Determining the underlying cause of these diseases—and of the often skewed sex ratio—is not proving easy.

One of the first things that scientists looked at for clues to explain the higher incidence in women than men of autoimmune disorders was whether diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) get better, worse, or stay the same during the menstrual cycle, pregnancy, and menopause. Although anecdotal reports vary, RA is the only one of these diseases in which a well-documented pattern appears during pregnancy. Frequently, RA improves while a woman is pregnant, and worsens again after delivery. Estrogen levels soar during pregnancy, but the studies that have been conducted to determine whether supplemental estrogen could ameliorate RA have yielded only negative results.

The effects of the menstrual cycle,

pregnancy, and menopause in other autoimmune diseases are inconsistent, casting doubt on the notion that fluctuating hormone levels can, alone, explain the female predominance of these disorders. High levels of female hormones like estrogen have traditionally been thought harmful to women with lupus, based in part on the long-time belief by many that pregnancy is deleterious for women with lupus. Limited data from more recent studies have caused researchers to question that notion, and NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has begun the first clinical trial on the safety of estrogens for women with SLE.

Researchers will conduct randomized, double-blind studies on the effects of hormone replacement therapy with estrogens and cyclic low-dose progestins in postmenopausal women with SLE and on the effects of oral contraceptives on disease activity in younger women with SLE.

Scientists Study Why More Women Are Affected Than Men

GENETICS AND THE COMPLEX INTERACTION WITH IMMUNITY

Though hormones play a role in the immune response, researchers are exploring other possibilities to explain the female predominance of autoimmune diseases. From the point of view of geneticists, autoimmune diseases are considered “complex”—the result of inheritance of many genes instead of just one, and an as-yet-unexplained interaction between these genes and the environment. These factors make it much more difficult to track inheritance of specific genes involved in an autoimmune disease than in other diseases that result from one gene acting with little or no environmental influence.

One lead came out of the observation that during pregnancy a mother’s immune system—normally programmed to reject any foreign tissue—tolerates the presence of a fetus, half of whose genetic make-up is from the father. The mechanisms of this “privileged” immune state of the fetus remain a mystery.

NIAMS-supported J. Lee Nelson at the Fred Hutchinson Cancer Research Center in Seattle, Washington, has used this natural anomaly as a starting point to investigate why RA often remits during pregnancy. In mothers with RA and their children, Dr. Nelson and coworkers investigated the genes that contain the molecular blueprint or code for HLA (human leukocyte antigen) proteins. These are the antigens on cell surfaces that enable the immune system to distinguish between the body’s own cells and those that are foreign. The presence of certain HLA genes has been found to be associated with susceptibility to some autoimmune diseases, including RA.

Dr. Nelson found that certain HLA gene markers were more frequently dissimilar between mother and child in pregnancies in which the mother’s RA improved. Without proposing a single specific mechanism, Nelson hypothesizes

that the mother’s immune response to the fetus may play a role in the improvement in RA during pregnancy.

Other studies are looking at the possible role of HLA compatibility between mother and child in scleroderma (a disease marked by thickening and hardening of the body’s connective tissues). Recent research supported by the National Institute of Child Health and Human Development found that fetal cells could persist in the bloodstream of the mother for as long as 27 years after birth. The peak incidence of scleroderma in women is between the ages of 35 to 54, just after the childbearing years. Dr. Nelson’s group is looking to see whether scleroderma—which shares some features with graft vs. host disease, an immune reaction of a donor’s transplanted cells to the tissues of the recipient of a bone marrow transplant—is more frequent in women whose HLA types are more similar to that of their offspring.

OTHER APPROACHES EXPLORED

Research continues to turn up clues of other mechanisms that might be at work to make women more vulnerable to autoimmune disorders. NIAMS-supported research on an animal model of lupus suggests that multiple genes convey susceptibility and shape exactly how the disease will manifest itself. NIAMS has also started a lupus registry in an effort to identify people with the disease as a resource for searching for genes involved in the origin of lupus. Results from human studies are beginning to shed light on the role of genes in determining susceptibility to SLE. National Institute of Neurological Disorders and Stroke-supported researchers are exploring differences seen under varying experimental conditions in the immune responses of female vs. male rats with an induced illness resembling multiple sclerosis. Scientists are also learning more about imprinting, in which the effects of genes

are altered by which parent—male or female—transmitted them to their offspring. There may be other gender-related effects on gene activation that play a role in autoimmunity.

A more complete understanding of why these diseases happen will eventually explain why women’s immune systems are more likely to turn on them—and how to prevent and treat the resulting illness. •

Charlotte Armstrong, writer/editor, Office of the Director, Office of Communications.

Autoimmune Diseases

Autoimmune diseases encompass a broad group of disorders, all marked by the immune system attacking normal tissue. The internal targets of autoimmune disease span the body’s systems and functions: rheumatoid arthritis (RA) affects the joints and joint linings, chronic active hepatitis and biliary cirrhosis damage liver function, insulin-dependent diabetes impairs sugar metabolism, and multiple sclerosis damages nerves. Systemic lupus erythematosus affects multiple organ systems.

Many, but not all of these diseases, affect more women than men. Multiple sclerosis (MS), RA, SLE, and thyroid disease, for example, affect as many as two, four, nine, and fifteen women, respectively, for every man. One notable exception is insulin dependent diabetes in which the male to female ratio is about one to one.

Paralleling the variety of target organs, research on these diseases cuts across NIH’s institutes. Efforts are under way to understand the types of immune cells that attack one’s own tissues, the antigens or protein targets of these cells, the triggers that set off the destructive process, and the genetics that convey predisposition. •

The NEXT



For years, people have talked about how different women and men are. Some have gone as far as to imply that women and men are from different planets. Yet, when it came to health care, women and men were often treated the same. Research would often be conducted on men, and then the results applied to the treatment of women and men of all ethnic and racial populations without any modification.

Today, health care providers and scientists recognize that a one-size-fits-all approach is not always appropriate. Women and men may require different treatments or interventions when it comes to their health care. The scientific community and the public at large have become more aware of women's health as a result of outreach efforts during the last decade. Researchers are paying more attention to all aspects of women's health, not just reproductive health. They are asking questions about a wide variety of topics that affect women's health, including normal development, early nutrition, breast cancer, cardiovascular disease, sexually transmitted diseases, autoimmune diseases, menopause, osteoporosis, behavioral risk factors, and many others. They are studying the entire life span, from prenatal through the elderly years.

"It has only been since the 1980s that the U.S. Public Health Service has directed specific and dedicated attention to women's health and research in eliminating gaps in knowledge about conditions that affect the health of women," says Dr. Vivian Pinn, Associate Director for Research on Women's Health and Director of the Office of Research on Women's Health at the National Institutes of Health. "Today, because of

the efforts of many dedicated advocates and scientists, we are beginning to make progress."

It is a well-known fact that women live an average of seven years longer than men, but the quality of this extended life may be compromised by chronic disease. Many women develop painful, debilitating, or life-threatening conditions such as osteoporosis, arthritis, breast or colorectal cancer, heart disease, urinary incontinence, or Alzheimer's disease. Researchers are working to learn more about when and why these conditions occur. They also are searching for reasons why men and women are affected differently by the aging process. By understanding causes of such conditions and normal processes, researchers can learn how to prevent and cure chronic diseases that affect

longevity. However, it is essential to study all those affected by it.

Heart attacks, for example, are the number one killer for both men and women. In fact, heart disease kills more women each year than all cancers, chronic lung disease, diabetes, accidents, and AIDS combined. But women tend to have heart attacks later in life than men, usually 10 years later, and they are often more fatal in women. By recognizing this variation, researchers can go a step further and determine why there is a difference. The results will be beneficial to the health of both women and men.

Heart disease is the leading cause of death for African-American, Hispanic, American Indian/Alaska Native, and white women. It is the second leading cause of death for Asian-American women. However, it may affect women

Phase

differently than men, and may not affect all women the same way. While more white women die from heart disease each year, African-American women tend to die from heart disease at a younger age.

Heart disease is not the only condition that affects some populations differently. Breast cancer, for example, has a higher incidence among white and Native-Hawaiian women than African-American women, yet the mortality rate is higher for African Americans. The incidence of breast cancer is lowest for Korean-American women. While 1991-95 statistics show a decline in the death rate for all women with breast cancer, this decline is more modest for African-American than for white or older women. Asian-American women have the lowest mortality rate from breast cancer of all women.

Researchers also are working to understand why diabetes is more common among African Americans and Native Americans than among whites; why twice as many African-American women as white women die from strokes; why the incidence of cervical cancer is twice as high for Hispanic women as non-Hispanic white women; and why the prevalence of tuberculosis is higher in the Asian population than the white population. As researchers continue to make strides in understanding the influencing factors that cause these variations, they are applying that knowledge to improve the prevention and treatment of these conditions.

Menopause is a universal phenomenon for women and can be natural, surgical or chemical in origin. There are more than 40 million postmenopausal women in the United States; by the year 2000, it is projected that there will be

more than 70 million postmenopausal women. Research is being directed to provide more answers about how best to maintain wellness in postmenopausal women and to minimize the reported health consequences of menopause.

Another current research initiative is a study of sex and gender differences in chronic pain. Our current knowledge highlights important questions that need further study. Past studies suggest that women exhibit lower pain thresholds, assign higher ratings of pain intensity to the same stimulus, and show lower pain tolerance than do men. Gender-based research is now yielding new insights and knowledge for more effective and safe approaches for treating acute or chronic pain and preventing pain-related disability in both women and men.

To answer these questions and many others, research studies must evaluate both men and women, and look at minority populations as well. The National Institutes of Health has a policy, strengthened by Federal law, requiring that women and minorities, as well as men, are included in all NIH-sponsored research (unless there is a valid, scientific reason to exclude a specific group). This policy enables researchers to compare how different populations are affected by a disease or condition, or how they respond to treatment or prevention methods. Once the differences are determined, the cause for these differences can be studied and applied to improving treatment and prevention methods for each affected population.

ORWH DEVELOPS A RESEARCH AGENDA

Six years ago, the NIH Office of Research on Women's Health developed

“OUR AGENDA

RECOGNIZES THE FULL

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FROM BASIC TO CLINICAL

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EPIDEMIOLOGICAL AND

POPULATION STUDIES,

CLINICAL APPLICATIONS

AND OUTCOMES.”

an agenda for women's health research. The agenda identifies where there are gaps in our knowledge and understanding of women's health, and in which areas NIH should develop more research efforts. With information gathered from public hearings and scientific workshops, ORWH continues to work with nationally renowned researchers, health care providers, women's health advocates, and the NIH research institutes to revise and update the agenda.

"Our agenda recognizes the full spectrum of research from basic to clinical research and trials, epidemiological and population studies, clinical applications and outcomes," Dr. Pinn says. "We have expanded the concepts of women's health and research to address the health of girls and women across the life span, recognizing that women's health encompasses more than the reproductive system during the childbearing years. Women's health extends from preconceptional health to chronic conditions of the elderly.

"As a result, NIH has initiated new research and enhanced ongoing studies to provide better information on sex and gender differences between women and men in normal development, health and disease; to identify factors that contribute to differences in the health status and health outcomes of women; and to focus clinical studies on populations of women that have previously been under represented in clinical research, such as minorities, women of differing socioeconomic status and geographic locations, lesbians, and women with disabilities."

The priorities of the women's health research agenda continuously changes as our understanding of women's health improves. As researchers answer some questions about a disease or condition, doors open with new questions that need to be answered. For example, researchers recently identified two breast cancer genes. Now they are determining the risks of developing breast cancer if the genes are present and the factors that influence development of the disease in the presence of such genetic mutations.

RESEARCH FOCUSES ON ENTIRE LIFE CYCLE

In studying women's health, it is essential to look at the entire life cycle. For example, osteoporosis affects 6-7 million postmenopausal women; another 12-17 million or one out of every two women over the age of 65 have such low bone density that they are at risk of developing osteoporosis. But research shows that the calcium a woman consumes in her younger years helps protect her against this condition later in life. Researchers recently released preliminary results of how much calcium a woman should consume and which years are most critical for retaining the calcium.

Addressing the health of young girls is a crucial step in learning how to prevent chronic conditions in later years. To this end, researchers are studying girls and boys as young as three years old who have a high risk of developing insulin-dependent, or juvenile onset, diabetes to better understand the gender differences in the progression of this disease. The study also is evaluating how a young girl's insulin requirements change with the menstrual cycle. With this new information, researchers are developing tests to predict who will acquire this disease, and treatments to delay or prevent it.

Another area of women's health that is currently being studied is the prevention of violence against women of all ages. Research is needed on the connection between family violence during a girl's childhood and subsequent risk-taking behaviors in adolescence.

Also central to research efforts in both basic science and clinical studies are health issues that are influenced by women's hormones and hormone-related health events in the lives of women, including menarche and menopause. Puberty and menopause are primary focuses for the research agenda.

Women today live approximately one third of their lives after menopause. It is more important than ever to be able to answer the many questions that women and their health care providers have about how to maintain good health during this time in their lives. A central

focus is hormone replacement therapy (HRT), its risks and benefits. More research is still needed to determine if long-term HRT reduces the risk of fractures caused by osteoporosis in addition to reducing the risk of heart disease. New studies also should clarify the increased risk, if any, for breast cancer.

As the number of elderly women increases, scientists need to better define aging in women. They need to determine the mechanisms—such as genetic, neuropsychiatric, psychological, immune, and hormonal—that differentiate men and women, and how these mechanisms affect health and longevity. For example, studies need to explore these differences between men and women in relation to factors such as body size and composition, drug metabolism, nutrition, and cerebral blood flow. Studies are also needed to determine the particular biological and psychological mechanisms that result in women's vulnerability to specific diseases and to frailty.

With the high incidence of autoimmune disease in women of all ages, research also is focusing on maternal-fetal tolerance to understand why the female body does not form antibodies to offspring but does attack its own tissue in such diseases as rheumatoid arthritis and systemic lupus erythematosus. Some new and innovative research initiatives on lupus were recently launched. Researchers understand that lupus results from an interaction between genetic, environmental, and hormonal factors. Many physicians do not prescribe oral contraceptives or HRT for women with lupus because of the widely held views that estrogens can aggravate the disease. Researchers are now examining the safety of estrogens for women with systemic lupus and are working to identify genes that determine susceptibility to the disease.

"While much remains to be done to address the many pressing questions about women's health," Dr. Pinn emphasizes, "it is all too easy to focus only on the gaps in knowledge that remain, forgetting where we started and how much progress has been made."

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The research agenda will continue to evolve and change as we move forward in our understanding of women's health. Hopefully, many of these questions will be answered as we enter the 21st century, but new questions will certainly arise. As our understanding of women's health increases, the quality of life for women, and their families, of all racial, ethnic, socioeconomic and other populations will continue to improve.

"Our goal is to make a difference for women's health in the 21st century," Dr. Pinn states, "through an improved research agenda that will foster studies that yield scientific data to lessen or eliminate continuing or emerging gaps in knowledge about women's health. To accomplish this goal, we must continue to ensure that women are included in clinical research and trials on conditions that affect their health, that women's health issues continue to receive attention by biomedical and behavioral researchers, and that there continue to be increased opportunities for women to enter biomedical research careers and advance to leadership and policymaking positions." •

*Ellyn J. Pollack, information officer, NIH
Office of Research on Women's Health.*

ORWH

Priority

Areas

The ORWH research priorities include basic, applied and clinical research on women's health. The research agenda focuses on leading causes of death in women, conditions that affect the quality of life of women, and normal or disease processes about which more knowledge is needed. Each year ORWH identifies priority areas for research that require more attention; current priorities include:

- Immunologic and arthritic diseases
- Acute and chronic pain conditions or syndromes
- Reproductive health, particularly: prevention, diagnosis, and treatment of pregnancy complications and embryo or fetus loss; reducing morbidity from myoma, endometriosis, abnormal uterine bleeding, uterine prolapse and other benign gynecologic diseases; and promoting increased safety and acceptability in the use of contraceptive options
- Sexually transmitted diseases and other infections, especially those involving emerging pathogens
- Urologic and renal health
- Gastrointestinal disorders
- The environmental impact on women's health
- Molecular bases for sex and gender differences in disease, including receptor populations and enzyme level differences, implications for unique pharmacokinetics and pharmacodynamics of medications in women, and the effects of hormone replacement therapy or oral contraceptives on the pharmacokinetics and pharmacodynamics of other medications
- Risk factors for diseases in women of different racial/ethnic/socioeconomic groups
- Factors associated with depression, eating disorders, anxiety, and addictive behaviors
- Risk factors and consequences of violence and trauma, including child abuse, physical and sexual assault, elder abuse, and domestic violence
- Behavioral and cultural factors in prevention strategies
- Lung cancer and/or tobacco use in women •



WOMEN OF ALL AGES SHARE THE PROBLEM OF URINARY INCONTINENCE—AND THEY MAY EVEN TALK AND JOKE ABOUT IT AMONG THEMSELVES—BUT NOT VERY MANY OF THEM SEEK MEDICAL HELP FOR IT.

WOMEN NEED TO KNOW THEY CAN DO SOMETHING ABOUT URINE LEAKAGE OR LOSS OF BLADDER CONTROL BECAUSE MANY TREATMENTS—FROM PELVIC FLOOR EXERCISES TO SURGERY—ARE AVAILABLE. THAT'S THE MESSAGE THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK) AND A PARTNERSHIP OF PROFESSIONAL AND PATIENT ADVOCACY GROUPS CONCERNED WITH URINARY INCONTINENCE ARE HIGHLIGHTING IN "LET'S TALK ABOUT BLADDER CONTROL FOR WOMEN," A NEW CAMPAIGN TO MAKE WOMEN AWARE THAT THIS COSTLY AND EMBARRASSING CONDITION IS TREATABLE.

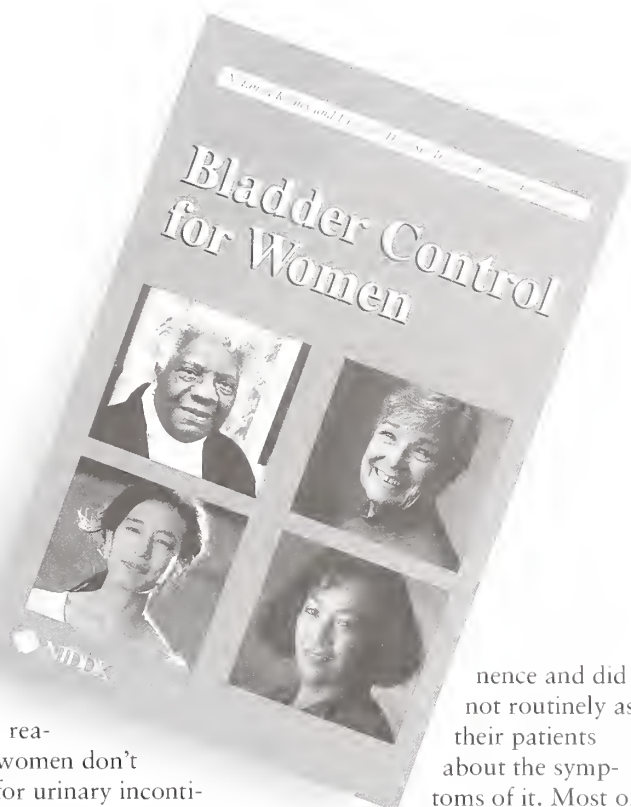
MEDICAL CARE CAN HELP WOMEN WITH URINARY INCONTINENCE

**PUBLIC EDUCATION
CAMPAIGN TARGETS
WOMEN AND
THEIR DOCTORS**

About 11 million of the 13 million Americans affected by urinary incontinence are women, according to the Federal government's Agency for Health Care Policy and Research (AHCPR). Urinary incontinence costs the United States \$16.4 billion per year by AHCPR's estimate, though some public health researchers estimate nearly double that figure.

"Urinary incontinence can have a hugely negative impact on the social and economic well-being of people who try to cope without seeking treatment," says Leroy Nyberg, Ph.D., M.D., director of the urology and women's health research programs for NIDDK. "They buy absorbent products; they may become reclusive." Some elderly people even become institutionalized unnecessarily because of urinary incontinence, Nyberg adds.

Meanwhile, the odds of improvement are excellent for women who seek treatment. But most women don't.



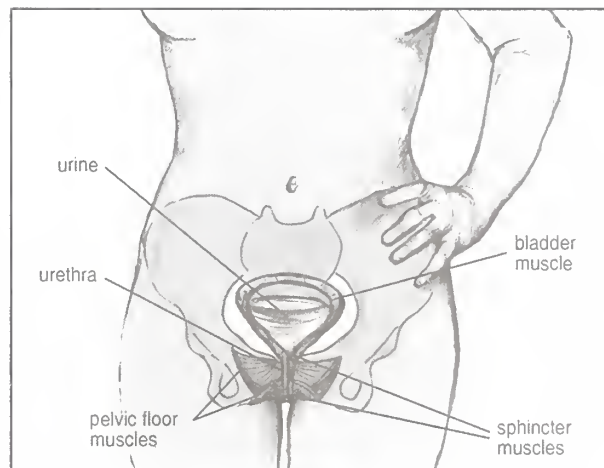
“There are several reasons why women don’t seek help for urinary incontinence,” according to Alan J. Wein, M.D., co-chair of the Bladder Health Council of the American Foundation for Urologic Disease and professor and chair of urology at the University of Pennsylvania Medical Center in Philadelphia. “Through a recent survey on women and incontinence, we learned that a quarter of the women surveyed feel embarrassed about urinary incontinence and are uncertain about dealing with the condition in social situations. Many women are unaware that a physician can help improve their condition or believe their problem isn’t severe enough to consult a physician.”

Also, many people, including many doctors, believe that incontinence occurs naturally with pregnancy, childbirth, menopause and aging. And many health care professionals lack the training to successfully treat urinary incontinence. A recent project funded by the Centers for Disease Control and Prevention (CDC) and AHCPR found that many physicians felt they did not know how to diagnose or treat urinary inconti-

nence and did not routinely ask their patients about the symptoms of it. Most of the physicians surveyed reported feeling that they should be more active in discussing incontinence with their patients.

The *Let’s Talk About Bladder Control for Women* awareness campaign offers easy-to-read booklets explaining the symptoms, types, and causes of poor bladder control as well as treatment options. The materials are designed to encourage and enhance communication between and among women and their health care providers. The goal of the campaign is to nudge more and more women into their doctors’ offices to tackle this problem head-on, without embarrassment.

Free consumer and health care provider kits are available by calling the NIDDK National Kidney and Urologic Diseases Information Clearinghouse at 1-800-891-5388. The materials are also online at <<http://www.niddk.nih.gov>>.



Parts of the bladder control system

The core partners in *Let’s Talk About Bladder Control for Women* are the American Uro-Gynecologic Association, American Urological Association, American Foundation for Urologic Disease, National Association For Continence, Society of Urologic Nurses and Associates, and the Simon Foundation for Continence. •

Kathy Kranzfelder, director, National Kidney and Urologic Diseases Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases.

Drug Addiction:

JAMIE,

A 28-YEAR-OLD WOMAN,
GOES OUT WITH HER NEW
BOYFRIEND TO HAVE A FEW
DRINKS AND SMOKE SOME
MARIJUANA. HE INTRODUCES
HER TO COCAINE AND
BEFORE SHE KNOWS IT SHE
IS SNIFFING, AND SOON
AFTER THAT SHE IS
FREEBASING COCAINE.

SALLY,

A SUCCESSFUL MIDDLE-AGED
BUSINESS WOMEN WITH A
PRESTIGIOUS JOB AT A LOCAL
COMPUTER COMPANY,
TAKES AMPHETAMINES ON
A REGULAR BASIS TO KEEP
UP WITH HER YOUNGER
COLLEAGUES.

These are just two of the many faces of drug addiction. Addiction, a chronic relapsing disease of the brain, affects all segments of the population. Directly or indirectly it touches the lives of everyone. It affects men, women, and children. In 1995, according to the National Household Survey on Drug Abuse, an estimated 12.8 million Americans or 6.1 percent of the population 12 years and older had used an illicit drug in the past month. Of those 12.8 million Americans, 4.3 million women ages 15-44 in 1995 had admitted to using an illicit drug in the past month. These statistics demonstrate that addiction is not just a man's disease.

Research shows that although there are fewer women than men who use drugs, the consequences of drug use are often quite different for males and females. For example, there is evidence that for several illicit drugs, such as marijuana, heroin, and cocaine, women may proceed more rapidly to addiction than do men. There is also evidence that nicotine dependence in females, relative to males, is controlled less by nicotine and more by psychosocial factors.

Past research on most health topics, including drug abuse and addiction, has been done almost exclusively on men; as a result relatively little data have been available on women. In recent years, however, the National Institute on Drug Abuse (NIDA) has encouraged research on drug abuse and women and gender differences. Preliminary data indicate that the progression and initiation to drug use and abuse, the consequences, as well as prevention and

Not Just a Man's Disease

treatment strategies may vary considerably between men and women.

The following areas are examples of what has been learned and what researchers are seeking to learn through NIDA research involving women and drug addiction.

WOMEN, DRUG ABUSE, AND HIV/AIDS

One of the most devastating consequences of illicit drug use for females is HIV/AIDS. AIDS is now the fourth leading cause of death among women 15 to 44 years and 64 percent of the AIDS cases among women are related to injection drug use (IDU). Among the total cases of pediatric AIDS in the United States, 54 percent are related to either maternal injection drug use or maternal sex with an injecting drug user.

The Centers for Disease Control and Prevention (CDC) surveillance data indicate that injection drug use continues to be a leading risk factor for HIV infection among women in the United States. Although these data may underestimate the true extent of HIV infection associated with injection or non-injection drug use, they nonetheless document the importance of drug use in generating new HIV infection. As of June 1996, 38 percent of identified HIV infection in adolescent and adult women was attributable to direct IDU (25 percent) or sex with an injection drug user (13 percent). Infection continues to increase in adolescent females and young women. As of June 1996, IDU or sex with an injection drug user accounted for 19 percent of HIV infection among females ages 13-19 and 26 percent among females ages 20-24.

Current research is addressing critical drug abuse issues in the clinical, immunologic, virologic, and behavioral aspects of HIV infection and disease in adult and adolescent females. Such data are essential in developing effective behavioral and medical interventions to reduce high-risk sexual and drug-using behaviors as well as HIV-associated morbidity. A series of studies are currently addressing gender roles and gender differences relating to drug-using behaviors, and sexual behaviors associated with drug use. Integrated long-term studies of biological and behavioral factors are examining the influence of drug use on the progression of HIV and the effectiveness of medical treatment. Research is also investigating the impact of drug use on maternal-infant HIV transmission, the course of disease in women and their infants, and treatment with HIV medications to reduce transmission.

PREGNANCY AND DRUG ABUSE

Of concern to NIDA and the nation is the use of drugs by women during pregnancy. Pregnant drug users may be at increased risk for miscarriage, stillbirth, low weight gain, anemia, thrombocytopenia (decrease in platelets), high blood pressure, and other medical problems. Their newborns may have lower birth weight and smaller head size than babies born to nondrug-using mothers. The NIDA National Pregnancy and Health Survey, the first survey to measure the prevalence of drug use among pregnant women, indicated that 5.5 percent, or 220,000, of the 4 million women who gave birth in 1992 used an

Women and Drug Abuse

- Overall, 7.3 percent (4.3 million) of women in their childbearing years (ages 15-44) in 1995 had used an illicit drug in the past month.
- An estimated 221,000 women who gave birth in the United States in 1992 used an illicit drug while they were pregnant.
- AIDS is now the fourth leading cause of death among women ages 25-44 in the United States.
- More than 50,000—about 64 percent—of the AIDS cases among women are drug related. •

illicit drug during pregnancy. Cocaine has been found to be the primary illicit drug problem of the majority of women of child-bearing age admitted to treatment in the past decade.

Research demonstrates that providing access to prenatal and other medical care can significantly improve birth outcomes for cocaine and polydrug exposed infants. Combining prenatal care with drug abuse treatment can result in increased weight gains and improved APGAR test scores, resulting in reductions in medical costs associated with low-birth-weight infants. Ultimately, interventions are needed to significantly reduce or stop drug use before pregnancy to improve pregnancy outcome.

Research-based model demonstration projects focusing on postpartum women and women with young children that

provide drug abuse treatment in combination with comprehensive “wrap-around” services shows that these women can be successfully treated for cocaine abuse and addiction. Two separate research demonstration projects have found that retention, an important predictor of treatment success, was improved by adapting treatment to meet the needs of the cocaine-dependent women who entered treatment. Adaptations included increasing the female-to-male ratio of both patients and staff, adding female-oriented therapy groups, and focusing on improved communication within the treatment program. It is reasonable to speculate that these treatment adaptations would be effective with all women independent of their parental status. These programs also found that women remained in treatment longer if their children lived with them than if they were separated from their children while in treatment.

BARRIERS TO TREATMENT

Despite the need and often the desire for treatment, women encounter special social, legal, and practical barriers in accessing drug treatment services. Many of these women are responsible for child rearing and most traditional therapeutic communities do not accommodate women with their children and/or pregnant women. When and if women do enter a treatment program, many are faced with leaving their children in the care of others, which they often can not afford, or understandably do not want.

The fear of legal sanctions and of losing custody of children is just one of several factors that impede women’s access to and successful engagement in drug abuse treatment. Male-dominated treatment settings (clients and staff) often overlook the concerns of particular importance to women—such as resolving issues of physical and sexual abuse, learning effective parenting, learning

how to deal with a pregnancy and the threat that drug use can have to the unborn child, and developing skills that will allow them to provide for themselves and their children.

Many treatment programs do not even accept pregnant women and may drop women from treatment if they become pregnant because they are unable to directly provide the prenatal medical services or the extensive support these women need. Prenatal care programs often do not have the resources to cope with the multiple social, medical, and other problems of drug-dependent pregnant women.

EFFECTIVE TREATMENT

NIDA has supported research that shows that treatment is effective for drug abusing women. The Drug Abuse Treatment Outcome Study (DATOS), for example, showed that women who had at least 28 days of treatment (at least 14 days in short-term inpatient) had sharp reductions in their use of illicit drugs, HIV-risk behavior, and illegal activities. For instance, 84 percent of the women who were admitted to long-term residential treatment programs admitted at intake using illegal drugs every day or at least once a week. Twelve months after treatment, only 28 percent continued to abuse drugs. Women who were receiving short-term treatment also showed significant reductions in illegal drug use a year after their treatment with 86 percent admitting use at intake and 32 percent reporting use after one year.

Because women have many specific needs, a number of components of treatment have been found to be important in attracting and retaining women in treatment. These include the availability of female-sensitive services; non-punitive and non-coercive treatment that incorporates supportive behavioral change approaches; and treatment for a wide range of medical problems, mental

TREATMENT PROGRAMS

SPECIFICALLY DESIGNED FOR

WOMEN SHOULD ALSO

TEACH CONFIDENCE, SELF-

ESTEEM, AND SELF

SUFFICIENCY.

disorders, and psychosocial problems. Treatment programs specifically designed for women should also teach confidence, self-esteem, and self sufficiency. One research study showed that treatment of drug-dependent women was more likely to be successful if treatment was provided in a mutually supportive therapeutic environment and addressed the following issues: psychopathology (e.g., depression); a woman’s role as mother; interpersonal relationships; and the need for parenting education.

FUTURE RESEARCH DIRECTIONS

Research on women will continue to play a significant role in NIDA’s overall research portfolio. As part of this effort, NIDA has begun to support a broad base of research aimed at investigating gender differences in the nature and extent of drug-using behaviors. This gender differences program involves NIDA’s full range of laboratory and field research aimed at identifying the consequences of drug use and abuse and determining the most effective treatment and prevention programs. The impact of drug use on pregnancy and on maternal functioning, including the effect of drug use on pregnancy outcome, the newborn, and the behavioral, intellectual and social development of children prenatally exposed, will also continue to be high priorities for NIDA. •

Robin Mackay, science writer, National Institute on Drug Abuse.

Cerebral Palsy Risks

Pregnancy



Cerebral palsy (CP), a group of chronic disorders characterized by impaired body movement and a loss of motor muscle control, currently affects more than 500,000 Americans. Each year approximately 4,500 American infants are diagnosed with cerebral palsy. Symptoms of CP may include shaking of limbs, loss of balance, inability to walk, seizures, and delay in growth and development. The disorder may also be linked to learning disabilities and mental retardation.

Although CP can be caused by an infection in the first month of life or by an injury in early childhood, most cases are *congenital*, or present at birth, and their cause is unknown. Through research, however, scientists have pinpointed some specific events during pregnancy or around the time of birth that can damage motor centers in the developing brain and increase the risk of CP. For example, infections that affect the mother during pregnancy such as rubella, cytomegalovirus, or toxoplasmosis may affect the fetus in the uterus, causing brain damage.

Research scientists have also uncovered certain characteristics, called *risk factors*, that increase the possibility that a child will later be diagnosed with CP. One risk factor is *low birth weight or premature birth*; the risk of CP is higher among babies who weigh less than 2,500 grams (5 lbs., 7½ oz.) at birth and among babies who are born less than 37 weeks into pregnancy.

ELECTRONIC MONITORING PROVIDES AN UP-TO-THE-MINUTE CHECK OF THE FETUS'S HEALTH. WHEN AN IRREGULAR HEARTBEAT IS DETECTED—WHICH MAY BE A SIGN OF TOO LITTLE OXYGEN—DOCTORS OFTEN PERFORM AN EMERGENCY CESAREAN SECTION IN AN EFFORT TO PREVENT BRAIN DAMAGE THAT CAN RESULT IN CP OR MENTAL RETARDATION.

Another risk factor is the existence of a *maternal disorder such as hyperthyroidism (overactive thyroid), mental retardation, or seizures*; mothers with any of these conditions are slightly more likely to have a child with CP than those without such conditions.

A healthy pregnancy, which can be achieved through regular prenatal care, good nutrition, and elimination of smoking, alcohol consumption, and drug abuse, should be the goal of every pregnant woman and her physician.

The National Institute of Neurological Disorders and Stroke (NINDS) conducts and supports research aimed at preventing CP. Much of this research focuses on discovering ways to lower the risk of CP during pregnancy and identifying and learning more about risk factors for the disorder. Three NINDS-supported studies are reported below.

MAGNESIUM SULFATE AND DECREASED RISK OF CP

In a study conducted by NINDS and the California Birth Defects Monitoring Program, investigators found that very low birth weight babies have a decreased incidence of CP when their mothers are treated with magnesium sulfate soon before giving birth.

Low birth weight babies are 100 times more likely to develop CP than normal birth weight infants. Magnesium is a natural compound responsible for numerous chemical processes within the body and brain. Obstetricians often administer magnesium sulfate, an inexpensive form of the compound, to pregnant women to prevent preterm labor and high blood pressure brought on by pregnancy. The drug, administered in-

travenously in the hospital, is considered safe when given under medical supervision.

The investigators concluded that magnesium sulfate helps reduce the risk of CP in very low birth weight infants. Despite these encouraging research findings, scientists warn, pregnant women should not change their magnesium intake. More research will be required to establish a definitive relationship between the drug and prevention of CP.

NEONATAL THYROID FUNCTION AND CP

In another study, scientists have linked low levels of a thyroid hormone in premature infants to the development of CP. The investigators examined more than 400 premature infants screened for blood levels of the hormone thyroxine during the first week of life and found that infants with low levels of thyroxine at birth had an increased incidence of CP at age 2.

The study, funded by NINDS and the National Institute of Child Health and Human Development, is the most comprehensive exploration of the relationship between low levels of thyroid hormone (a condition called *hypothyroxinemia*) at birth and neurodevelopment in premature infants. Premature infants often go through a period of transient hypothyroxinemia. In most cases, including those in which CP is indicated, thyroid function returns to normal within a few weeks or months.

Although this finding raises optimism that the risk of CP in children can be reduced, more research is needed to determine if treatment with thyroid hormone will prevent abnormalities in prenatal brain development that lead to CP.

FETAL MONITORING AND RISK OF CP

Recently, in a large study funded by NINDS, investigators found that electronic fetal heartbeat monitoring during delivery is not helpful in preventing CP and may lead to a higher rate of potentially dangerous cesarean sections.

Electronic monitoring provides an up-to-the-minute check of the fetus's health. When an irregular heartbeat is detected—which may be a sign of too little oxygen—doctors often perform an emergency cesarean section in an effort to prevent brain damage that can result in CP or mental retardation.

Results from the study revealed that of every 100,000 babies monitored during birth, 9,300 will have abnormal heartbeats. Yet just 18 of these babies will be expected to have CP. Due to the false alarms, however, many of the 9,300 mothers will be rushed to the operating room for cesarean sections. About 4 percent of these operations will result in serious complications for the mother, such as bleeding and infection. The researchers concluded that in most cases electronic monitoring may be more risky than beneficial.

Further, the researchers found that performing a cesarean section does not prevent CP. Among the babies who had ominous signs during monitoring, those delivered by cesarean section did not have a lower frequency of CP than those delivered vaginally.

These findings reinforce other research, discussed earlier, showing that most CP cases can be traced to events such as maternal infections early in pregnancy that may damage the fetus' central nervous system.

Research conducted and supported by NINDS continuously seeks to uncover new clues about CP. As investigators learn more about the causes of CP through basic and clinical research, doctors and parents will be better equipped to help prevent this disorder. The ultimate hope for overcoming CP lies with prevention.

For a copy of the NINDS publication, "Cerebral Palsy: Hope Through Research," please write or call: NIH Neurological Institute, P.O. Box 5801, Bethesda, Maryland 20824, (301) 496-5751. •

*Shannon E. Garnett, writer/editor,
National Institute of Neurological
Disorders and Stroke.*



As a first-year graduate student at the University of Wisconsin-Madison, Michelle Bennett was beginning to see the future more clearly. She pictured a fulfilling career in basic research, one that would benefit those who are suffering from illness and disease. And she knew she had the tools to make that dream come alive—a keen interest in science, a strong work ethic, and the ability to make the most of the opportunities that came her way.

But never in her wildest dreams could she have imagined that just months after receiving her degree, she would be accepted for a postdoctoral position with NIH's National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, and get the chance to do some cutting-edge biomedical research in molecular genetics. Or that just one year later, she would play a pivotal role in the internationally acclaimed discovery of BRCA1, the first gene shown to be responsible for inherited breast and ovarian cancer.

But what Bennett finds even more remarkable is that she has just been awarded a three-year, \$120,000 medical research grant from the U.S. Army to develop a genetically engineered strain of mice that will have defective copies of a second breast cancer gene, BRCA2, that has been linked to the majority of inherited breast cancers not caused by BRCA1. NIEHS investigators will use

NIEHS Researcher Breaks New Ground in the Fight Against Breast Cancer

the mice to learn more about how hereditary breast cancer develops in humans.

While these accomplishments have validated her career as a scientist, Bennett credits her early years as an undergraduate as having pointed her in the right direction. "During my first couple of years at Kalamazoo College, I spent a quarter doing administrative work for Illinois Senator Charles Percy—reading

Dr. Michelle Bennett

mail, answering the phone," says Bennett. "While the experience didn't have a direct impact on my career, it helped me realize I didn't want to go into politics!"

BENNETT EXPLORES A CAREER IN RESEARCH

Although Bennett had tentatively set her sights on becoming a doctor, she wanted to find out more about the world of laboratory research. During her senior year, she took a quarter off to do an independent project with Upjohn, a pharmaceutical company in the area. Her mentor was Leonard Post, a



molecular biologist who was working on a strain of

herpes virus that infects pigs. The virus is very similar to the one that causes cold sores in humans. "That experience was the real turning point for me," recalls Bennett. "The fact that we were working on a vaccination that might protect the pigs from getting this virus was incredibly exciting."

With her goals more clearly mapped out, Bennett enrolled at the University of Wisconsin-Madison for graduate study in cancer genetics and a chance to work with Norman Drinkwater, one of the country's most renowned molecular biologists. Under Drinkwater's tutelage, Bennett learned the intricacies of gene mapping, a powerful gene-finding approach that was being used by the NIEHS scientists in their search for the breast cancer gene. "When I interviewed for a position with NIEHS, I realized my training and experience were ideally suited to the project they were working on," says Bennett.

By the time Bennett joined the NIEHS team in 1993, the effort to pinpoint the location of BRCA1 was already well underway. The gene had been traced to a specific region of chromosome 17, and lead investigators Roger Wiseman and Andrew Futreal were looking at breast tissue samples taken from healthy women in an effort to find a "candidate gene"—that is, a gene that they suspected might be BRCA1.

The researchers then compared these normal genes with the same genes taken from breast tumor samples of women known to be genetically predisposed to breast cancer. "Analysis of the tumor

samples revealed a specific gene that was somehow different from its 'normal' counterpart," says Bennett. "When we found this same pattern of alterations in subsequent samples, we began to feel confident that we had found BRCA1."

Bennett's job was to "organize" the bits and pieces of DNA obtained from pools of DNA sequences into recognizable pictures of potential genes that could be used in the comparisons. "Gene mapping is a bit like fishing from a lake that contains many different species of fish," explains Bennett. "Some of the fish taken from the lake are easily identified, while others are curious specimens that the fisherman has never seen before. The fisherman must then draw upon the information he gets from both kinds of fish in order to find what he is looking for."

Bennett remembers how easy it was to get caught up in the excitement of the gene discovery and its immediate impact—the possibility of a long-awaited test that could identify those at greatest risk for developing inherited breast cancer, international recognition for her and her colleagues, and unprecedented publicity for NIEHS. But in the years since the breakthrough, some of Bennett's enthusiasm has given way to caution. "I can picture the day when everyone will carry an identification card that lists their genetic history," she says. "The social, legal, and ethical ramifications of this would be enormous."

RESEARCHERS STUDY ROLE OF BRCA2 GENE

In spite of these recent advances, scientists do not yet understand how a single gene like BRCA1 can influence a process as complex as breast cancer. With the discovery of the second breast cancer

gene (BRCA2) by Futreal, now with the Duke Comprehensive Cancer Center, and a host of other collaborators, those answers may be close at hand. "We know that women who inherit a defective copy of BRCA2 from one parent have an 80 to 90 percent chance of developing breast cancer during their lifetime," explains Bennett. "Now we want to know what makes this gene so critical."

In order to answer this question, Bennett will attempt to breed a line of genetically engineered mice that are "BRCA2-deficient"—that is, mice that carry one or two defective copies of their BRCA2 genes. She will then compare their growth and development with that of normal mice, looking for differences that can be attributed to the faulty gene. These differences may help to unlock some of the secrets about how the gene works and what happens when it doesn't. "We should eventually be able to design studies that can identify some of the environmental factors and lifestyle practices that influence breast cancer development in genetically predisposed individuals," says Bennett.

And what kind of future does Bennett picture five years from now? "That's a very difficult question to answer because cancer research is such a highly competitive field," she admits. "Right now, I have two small boys—Kyle and Parker—who need a lot of my attention. Once they get a bit older, I would enjoy having a lab of my own. I have also thought a lot about teaching. I think it is important that our young people understand how exciting and fulfilling a science career can be." •

*John Peterson, public affairs specialist,
National Institute of Environmental
Health Sciences.*

NIDDK Encourages African- American Women to

MOVE MORE AND EAT BETTER

HEALTH AWARENESS CAMPAIGN EMPHASIZES WALKING PROGRAM

RISING WITH THE SEPTEMBER
 SUN TO CELEBRATE
 "SISTERHOOD" AND HEALTHIER
 LIVING, 100 AFRICAN-
 AMERICAN WOMEN FROM
 THE BOSTON NEIGHBOR-
 HOODS OF DORCHESTER,
 MATTAPAN, AND ROXBURY
 PARTICIPATED IN A 2-MILE WALK
 AND WELLNESS FAIR AT THE
 REGGIE LEWIS TRACK AND
 ATHLETIC CENTER IN BOSTON.
 SINCE THAT KICK-OFF
 MORNING IN 1995, MANY
 HAVE CONTINUED TO WALK
 IN AND AROUND THEIR
 COMMUNITIES FOR BETTER
 HEALTH AND FITNESS.

How do I warm up?
Bench. Perform slow movements and stretch only as far as you feel comfortable.

Side Reaches
Reach one arm over your head and to the side. Keep your hips steady and your shoulders and your shoulders straight to the side. Hold for 10 seconds and repeat on the other side.

Knee Pull
Lean your back against a wall. Keep your head, hips and feet in a straight line. Pull one knee to your chest, hold for 10 seconds, then repeat with the other leg.

Wall Push
Lean your hands on a wall with your feet about 3-4 feet away from the wall. Bend one knee and point it toward the wall. Keep your back leg straight with your foot flat and your toes pointed straight ahead. Hold for 10 seconds and repeat with the other leg.

Leg Curl
Pull your foot to your buttocks with your opposite hand. Keep your knee pointing straight to the ground. Hold for 10 seconds and repeat with the other foot.

Taking the First Step
Walking right is very important.
Walk with your chin up and your shoulders hold slightly back.
Walk so that the heel of your foot touches the ground first. Roll your weight forward.
Walk with your toes pointed forward.
Swing your arms as you walk.

A sample walking program

Week	Walk slowly	Walk briskly	Walk slowly	Walk slowly
WEEK 1	4 min	4 min	4 min	4 min
WEEK 2	4 min	4 min	4 min	4 min
WEEK 3	4 min	4 min	4 min	4 min
WEEK 4	4 min	4 min	4 min	4 min
WEEK 5	4 min	4 min	4 min	4 min
WEEK 6	4 min	4 min	4 min	4 min
WEEK 7	4 min	4 min	4 min	4 min
WEEK 8	4 min	4 min	4 min	4 min
WEEK 9	4 min	4 min	4 min	4 min
WEEK 10	4 min	4 min	4 min	4 min

Walking
MOVE MORE EAT BETTER
CALL 1-800-WIN-8098 for more information on the SISTERS Together Program

They walk and wellness fair officially launched the *Sisters Together: Move More, Eat Better* campaign, a 3-year pilot health awareness program for Boston-based African-American women ages 18-35. *Sisters Together* is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) Weight-control Information Network (WIN), a clearinghouse that provides up-to-date, science-based information about obesity, nutrition, physical activity, and related nutritional

disorders to health professionals, the media, and consumers.
 "Walking is an activity that everyone can enjoy," says Nellie Knight, community health coordinator and Boston *Sisters Together* Advisory Group member. "No special skills or talents are required for walking."
 The walking groups meet 5 times a week and walk 1 to 2 miles. During the winter, an indoor walking site, the Shelburne Center, is reserved. Women from the three Boston communities are regularly recruited and trained to serve as walking group leaders. Group leaders share with fellow walkers information



about

the importance of regular physical activity and distribute *Walking* brochures to group members.

The four panel, pumpkin and purple brochure, which the target audience selected because of its vibrant colors and complimentary images of black women, explains the health benefits of walking, safety tips for walkers, examples of warm-up exercises, and a sample walking program.

"*Sisters Together* is providing women a chance to take small, achievable steps that will improve their health over a lifetime," says Rima Rudd, Sc.D., of the Harvard School of Public Health and *Sisters Together* advisor.

HEALTHY PRACTICES AIMED AT PREVENTING WEIGHT GAIN

The Third National Health and Nutrition Examination Survey (NHANES, III) indicates that nearly 50 percent of African-American women over the age of 20 in the United States are overweight, which is a major risk factor for diabetes, heart disease, high blood pressure, and some cancers.

"The adverse health outcomes for African-American women who are overweight are well documented," says William Dietz, M.D., Ph.D., director of clinical and pediatric nutrition at the New England Medical Center and coordinator of *Sisters Together*. "Our challenge now is to discover, with their help, what lifestyle changes African-American women need to make and maintain that will keep them from becoming overweight."

To promote the campaign's "eat better" message, all participants received

the 1996 *Sisters Together* wall calendar. From "Spicy Black Bean Soup" to "Quick 'n' Simple Peach Crisp," each month the calendar features a healthy, easy-to-prepare recipe from one of the Food Guide Pyramid's five food groups. The calendar also provides menu planning tips, nutrition and physical activity information, and space to keep a daily record of activities. Based on positive feedback from campaign participants, the Advisory Board is considering printing a 1998 calendar using the current structure and updating the look with new colors and recipes.

Research of African-American women's knowledge, attitudes, and practices related to diet and physical activity is the foundation for *Sisters Together* materials and activities. Many of the women described healthy foods as those that are "good" for you and those you "should" eat. They identified a variety of produce as healthy, including broccoli, greens, carrots, apples, and oranges. Beef, chicken, fish, and seafood are also considered healthy foods. Some women also view dairy products, particularly cheese, as healthy. Many survey participants define physical activity as any movement of the body. Walking is the most popular and beneficial activity because it is easy, non-competitive and can be done with friends and family members. The women surveyed also like basketball, dancing, roller skating, and softball.

To further reinforce the "eat better" message, in 1996, the campaign also sponsored "What's Cooking in the Neighborhood," a 15-minute segment of the Boston live cable show, "Today's Living." The segments, hosted by nutritionist and Boston Advisory Group member Donna DeCaille, featured healthy cooking demonstrations by chefs from Dorchester, Mattapan, and

Roxbury restaurants. The segments highlighted such dishes as "Jerk Chicken," "Rice 'n' Beans," and "Curried Chicken."

According to DeCaille, "The chefs really enjoyed the chance to show the community how to prepare healthier versions of some popular and traditional dishes. The viewers also appreciated the "how-to" information to guide them."

Community involvement and partnership activities with the campaign are growing. Boston-based programs and organizations, including Body by Brandy, the Expanded Food and Nutrition Education Program, the Mattapan Neighborhood Health Center, the Roxbury Heart Center, local Farmers' Markets, and local Head Start groups are actively working with *Sisters Together* to encourage women within the targeted population to improve their health by eating better and increasing physical activity. Local hair salons, YMCAs, and grocery stores are also interested in distributing *Sisters Together* educational and promotional materials to their clientele. "Community interest and participation, thus far, has been key to the campaign's initial success and will be essential to any future success," says Dietz.

The NIDDK-funded Boston Obesity/Nutrition Research Center, which includes representatives from the New England Medical Center, the Harvard School of Public Health, and Tufts University School of Nutrition Science and Policy, directs the Boston-based campaign. •

Leslie L. Curtis, director, Weight-control Information Network, National Institute of Diabetes and Digestive and Kidney Diseases.

DR. LUCY SHAPIRO:

PROBING THE SECRETS OF EARLY DEVELOPMENT



Dr. Lucy Shapiro, Professor and Chair of the Department of Developmental Biology at the Stanford University School of Medicine

One of the most intriguing questions in human biology is how one cell, a fertilized egg, divides and develops into a healthy baby. What tells some cells to mass together into a liver; others to form bones, or skin, or eyes; others to wind around organs as blood vessels and nerves? And what prevents—in the vast majority of cases—defects in this developmental process?

Like most interesting biological questions, these are far too complex to answer by direct study of developing human embryos (to say nothing of the ethical issues involved). Because many of the genes and physiological pathways that govern life are similar among all living organisms, researchers can answer some of their questions by studying simpler systems—such as frog eggs, fruit flies, or bacteria. The lessons they learn from these simpler “model systems”

often provide information about more complex organisms, including humans.

Dr. Lucy Shapiro, a developmental biologist at the Stanford University School of Medicine, is trying to determine the rules that dictate a cell’s specialization. She seeks to understand how a cell uses a biochemical blueprint—its genetic code—to develop into a mature cell with specific structures and properties. Dr. Shapiro’s work has revealed how some bacteria control their cell division cycle and how they distinguish which end is “up,” which is necessary for normal cell development.

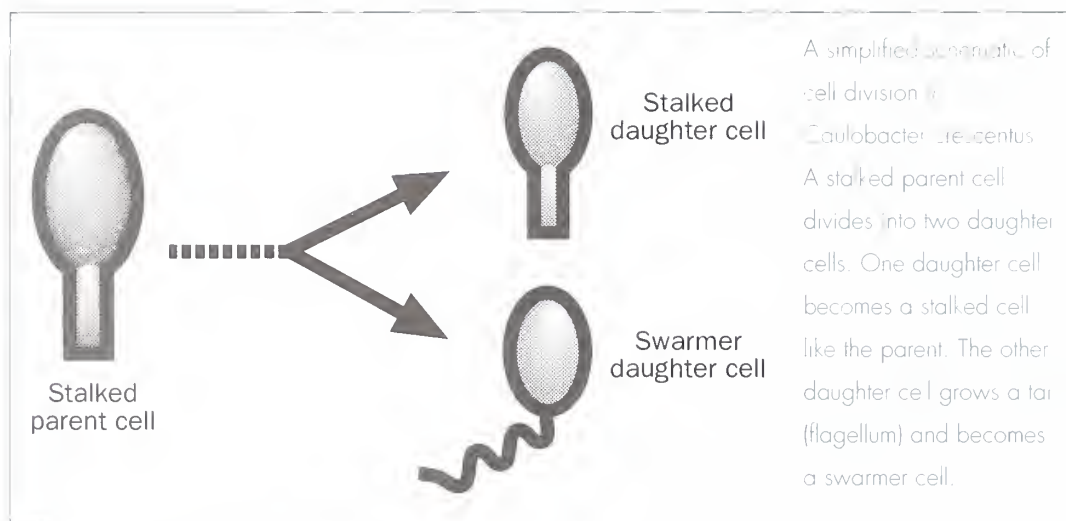
Because her research seeks to unravel the fundamental laws of nature, rather than to address a specific medical concern, it is supported by the National Institute of General Medical Sciences, the “basic research institute” of the National Institutes of Health. Unexpectedly,

her basic research also has opened doors to potential new antibiotics for humans and livestock, as well as potential pesticides for fruit trees and vines.

RESEARCH INVOLVES SINGLE-CELL ORGANISM

Dr. Shapiro conducts her studies using a single-celled, aquatic bacterium called *Caulobacter crescentus*. This bacterium possesses an interesting property that makes it a perfect choice for Dr. Shapiro’s research. When each cell is ready to divide, it resembles a tiny, oblong mushroom with a head and a stalk. After cell division, the two resulting daughter cells have different fates—one becomes a “stalked” cell, resembling the parent; the other grows a tail, becomes a “swarmer” cell, and swims away. *Caulobacter* thus accomplishes the feat that underlies all development—

NIH-Supported Scientist on the Forefront of Basic Research



it generates daughter cells that differ from the parent cell.

To understand how cells control their final identity, Dr. Shapiro examines how *Caulobacter* builds its whip-like tail, called a flagellum. This tail has to be built at precisely the same time every generation, so she uses it as a marker to measure the specialization of “swarmer” cells.

The development of *Caulobacter* and all other cells is controlled with an elaborate, multi-step process called the cell cycle. Just as levels of hormones control the timing and rate of human development during adolescence, fluctuating levels of specific molecules within a cell control its progress through the cell cycle.

The climax of the cell cycle is cell division, when one cell splits into two. This is a critical and tightly controlled process. In humans, when cell division—or other stages in the cell cycle—escape their built-in controls, serious medical problems, including cancer, may result. Many researchers believe that decipher-

ing which molecules regulate development and cell division will aid the design of new anticancer therapies.

STUDIES MAY LEAD TO NEW ANTIBIOTICS

Recently, Dr. Shapiro discovered that one protein, called CtrA, controls in *Caulobacter* what is arguably the most critical step in cell division—the beginning of DNA replication. At this stage, the cell’s genetic material is copied so it can be evenly distributed between the two daughter cells. In addition to controlling chromosomal replication, CtrA is the “hub” of a genetic network that regulates many essential cellular functions. Studying the gene for CtrA will not only help scientists decipher these genetic functions in bacterial cells, but also may have more immediate applications in the development of new antibiotics.

Without CtrA, *Caulobacter* cells cannot survive. In other words, CtrA is essential for *Caulobacter* life. With that discovery, some of Dr. Shapiro’s research took a turn toward the pharmaceutical

industry. Any protein that is required for bacterial viability is a potential target for antibiotic drugs.

Previously, she and her colleagues found another protein that is essential for the life of *Caulobacter*. This protein, called DNA methyltransferase (CcrM), chemically tags the bacteria’s DNA in a way that enables it to function normally. Like many other essential cell cycle genes, the CcrM gene is “turned on” by CtrA.

Dr. Shapiro’s group learned that at least three other bac-

teria—*Brucella abortus*, *Agrobacterium tumefaciens*, and *Rhizobium meliloti*—also require CtrA and CcrM. Although *Caulobacter* is harmless, two of these other bacteria are not so benign. *Brucella abortus* causes disease in livestock and can be transmitted to humans. *Agrobacterium tumefaciens* causes serious disease in plants, especially grapevines and fruit trees. *Rhizobium meliloti* acts as a bacterial fertilizer on the roots of alfalfa. It is beneficial to the plants and harmless to humans and animals.

Now Dr. Shapiro has access to four bacterial model systems—including ones with immediate relevance to agriculture—in which to study the critical CtrA and CcrM proteins. What began as academic research into basic biological questions now has potentially significant economic and agricultural implications.

Realizing that the breadth of the research had outgrown her lab, she established a consortium of scientists to study the function of the genes for CtrA and CcrM in disease-causing bacteria. Some of the consortium scientists are experts

WHY

Do Basic Research?

"WHAT WE HAVE HERE IS A WHOLE NEW APPLIED OUTCOME OF VERY, VERY BASIC RESEARCH," DR. SHAPIRO SAYS. "AND I'M WILLING TO MAKE YOU A BET THAT WE COME UP WITH A WHOLE NEW CLASS OF ANTIBIOTICS."

on *Brucella* bacteria, others study the plants infected by *Agrobacterium*, still another works with live animals infected with *Brucella*. Now, consortium chemists in collaboration with pharmaceutical companies are working to design drugs that target and block these critical proteins, with the hope that their efforts will lead the way to new antibiotics.

"What we have here is a whole new applied outcome of very, very basic research," Dr. Shapiro says. "And I'm willing to make you a bet that we come up with a whole new class of antibiotics."

In the meantime, the scientists are continuing to learn more about what controls cellular differentiation and progress through the cell cycle. Dr. Shapiro's most recent paper proves that bacterial life cycles are controlled by the same general processes that regulate human cells. This knowledge brings us ever closer to answering the fundamental biological question: How does one cell become a complex, living organism? •

Alisa Zapp, science writer, National Institute of General Medical Sciences.

Basic research, such as that supported by the National Institute of General Medical Sciences, supplies the foundation for the clinical advances that improve the health of both women and men. Often the effects of advances in basic research are first felt in the laboratory, where they yield new tools and concepts that permit more sophisticated experiments to be conducted. These experiments, in turn, enable researchers to devise new drugs and treatments for various disorders.

An excellent example of the impact of basic research is the development of recombinant DNA technology. This term refers to a body of techniques, developed in the 1970s, for cutting apart and splicing together different pieces of DNA. When segments of human or animal DNA are transferred into another cell line or organism, the substance for which they code may be produced along with substances coded for by the native genetic material of the cell line or organism. The cells then become "factories" for the production of the protein coded for by the inserted DNA. This technology grew from untargeted studies of the fundamental nature of DNA—untargeted because, although the researchers knew DNA was critical to life, they did not know precisely where their research would lead.

Recombinant DNA technology greatly expanded the types of experiments scientists could conduct. It also formed the basis for a host of new biotechnology companies that are now producing commercially important products to treat many disorders. For

instance, one "biotech" product, tPA, which is used extensively to break up blood clots in people who have had heart attacks, has recently been found to also be helpful in preventing many of the long-term disabilities that occur after a stroke.

One of the most significant aspects of basic research is that advances in the understanding of fundamental processes usually lead to many types of practical applications. For instance, the discovery of ways to cut DNA at specific sites not only enabled researchers to develop recombinant DNA technology and make new drugs, it also permitted them to cut fragments of DNA and compare them in families with a history of genetic disease. This comparison, in turn, helped researchers find the genes involved in a number of genetic diseases. The list of newly-found disease genes is growing every year—and, of course, it includes many genes for diseases that affect primarily women, such as those for breast cancer.

Advances in basic research are usually the result of many years of continuing study in a relatively narrow field. Dr. Shapiro, for instance, has studied *Caulobacter* since 1966. Although occasionally basic researchers make important discoveries unexpectedly, most breakthroughs would not be possible without years of hard work. "Chance," as Louis Pasteur said, "favors only the mind that is prepared." •

Doris Brody, public affairs specialist, National Institute of General Medical Sciences.

BETTER DIAGNOSIS AND
TREATMENT AVAILABLE FOR
THOSE WHO SEEK HELP

Hopeful

News for Women

It's coming again.

You're sure you're about to have another episode.

Do you have terrifying moments like these? You may have Panic Disorder. And once it is diagnosed, treatment is available. For more information, call **1-800-64-PANIC**.

It's

The most frightening thing about having Panic Disorder is not knowing when it's coming back.

Repeated episodes of shooting chest pains. Racing heart. Overwhelming fear. It could be many things, but all the medical tests show nothing is wrong. That's when it's time to ask, "Could this be Panic Disorder?"

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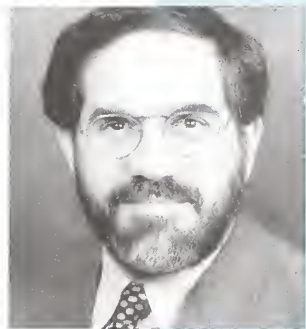
Public Awareness Campaign
includes publications and other
materials specifically aimed at
women.

Suffering from Mental Disorders

TIPPER GORE, WIFE OF VICE PRESIDENT ALBERT GORE AND STAUNCH SUPPORTER OF TREATMENT FOR MENTAL DISORDERS, KNOWS DEPRESSION. HER MOTHER SUFFERED FROM IT WHEN SHE WAS GROWING UP. "THIS WAS BAD ENOUGH, BUT THE SITUATION WAS MADE WORSE BY HER FEARS THAT SOMEONE WOULD FIND OUT," GORE WRITES IN HER NEW BOOK, PICTURE THIS: A VISUAL DIARY. "IT BROKE MY HEART," SHE SAYS. "FOR DECADES, SHE SUFFERED IN SILENCE."

The experience of Tipper Gore's mother is not uncommon. In the United States, more than 17 million people, most of them women, experience depression each year, according to the National Institute of Mental Health (NIMH).

"Nearly two thirds of people with depression do not get the help they need," says NIMH Director Dr. Steven Hyman. People suffering from anxiety



Dr. Steven Hyman

Treatment Works

Today, successful treatments developed through research allow millions of people with mental disorders to live full, productive lives. Treatments for depression, anxiety disorders, and eating disorders often involve medication, specific forms of psychotherapy, or a combination of the two.

Medications, although not cures, can be very effective at relieving symptoms. Today, thanks to research by investigators at NIMH and other research institutions, there are many medications available. So, if one drug is not successful another can be tried.

Research has also shown that behavioral therapy or cognitive-behavioral therapy can be

effective for treating depression, several of the anxiety disorders, and eating disorders. Behavioral therapy focuses on changing specific actions and uses several techniques to decrease or stop unwanted, problematic, painful, or stressful behaviors. For example, one behavioral technique trains patients with anxiety disorders in diaphragmatic breathing, a special breathing exercise involving slow, deep breaths to reduce anxiety. This is necessary because people who are anxious often hyperventilate, taking rapid shallow breaths that can trigger rapid heartbeat, lightheadedness, and other symptoms. Other behavioral techniques include assertiveness training and role playing.

Like behavioral therapy, cognitive-behavioral therapy teaches patients to react differently to situations. However, patients also learn to understand how their thinking patterns contribute to their symptoms and how to change their

thoughts so that symptoms are less likely to occur. Cognitive-behavioral therapy for depression focuses on changing the negative styles of thinking and behaving that are common among depressed people. By helping patients tackle their negative thoughts about themselves, their world, and the future, cognitive-behavioral therapy encourages behaviors that engender hope and pleasure and elicit positive responses from others.

Other forms of psychotherapy, such as interpersonal therapy, which focuses on disturbed social relationships, have also been proven helpful in treating some of these disorders. •

disorders, eating disorders, and other mental illnesses often fail to get treatment as well. Some fear the stigma associated with mental illness. Others deny that they have a problem or lack the energy or hope for the future that is needed to take the initiative to get treatment. Still others view their symptoms as punishment or their own fault. And sometimes doctors and other health care professionals fail to recognize and treat depression and other mental disorders.

Yet, effective treatments are available for many disorders. Treatment can help people who suffer from depression symptoms, which last weeks, months, or even years and include extreme sadness and hopelessness; decreased energy; difficulty sleeping, concentrating, and making decisions; and thoughts of death or suicide. "Treatment can help 80 percent of people affected by depression," Dr. Hyman says. And there is similar good news for other disorders.

"Today we have more knowledge than ever before about the diagnosis and treatment of mental disorders," he says. "Research has yielded an impressive armamentarium of new medications with fewer side effects as well as specific psychotherapies that can help many people." For example, for an anxiety disorder called panic disorder, treatment—medications or cognitive-behavioral psychotherapy—can improve the lives of 70 to 90 percent of people, mostly women, suffering from the disorder.



Dr. Delores Parron

WOMEN AFFECTED MORE THAN MEN

Women often have care-giving responsibilities for their parents as well as their children. When women have mental health problems, it can affect the well-being of three generations.

Why certain mental disorders such as depression, anxiety disorders, and eating disorders affect more women than men is part of an intense, NIMH-supported research effort. Sophisticated epidemiological studies have provided a clear picture of the specific differences in the prevalence of these disorders between men and women. "There are neurodevelopmental, hormonal, and sociocultural influences that affect these conditions," says Dr. Hyman.

"Gender has been recognized as a powerful factor in the manifestation and treatment of these and other mental dis-

orders," says Dr. Delores Parron, NIMH associate director for special populations, who coordinates the Institute-wide, \$102 million research program related to the mental health of women.

Before adolescence and late in life, females and males experience depression with the same frequency, according to epidemiological research. Because the gender difference in depression is not expressed until after puberty and ends following menopause, it is hypothesized that hormonal factors are involved in women's greater vulnerability. "Gender influences the risk of depression, but does not cause it," says Dr. Hyman. Stressors due to psychosocial factors—such as multiple roles in the home and at work and the increased likeli-

hood of women, compared to men, to be poor, at risk for violence and abuse, and raising children alone—also play a role in the genesis of depression and other mental disorders. It is important to note, Dr. Parron says, that depression and other disorders such as anxiety disorders, eating disorders, and substance abuse often occur in conjunction with one another.

SCIENTISTS STUDY GENETICS AND ENVIRONMENT

NIMH-funded scientists are increasingly turning to the study of the interplay between genes and environment to understand the causes of mental illnesses.

"Research advances indicate that depression and anxiety disorders arise as a combination of a genetic vulnerability with an environmental second hit," says Dr. Hyman.

DIFFERENCES

Between Women and Men

The environmental hit in depression could be stressful life events. One recent study examined more than 1,000 pairs of female twins and found four life experiences that predicted the onset of depression with odds greater than 10 to 1. Women who experienced the death of a close relative, assault, serious marital problems, or divorce/breakup were more likely to develop depression, especially if their twin also had depression. Evidence is also emerging that other disorders, such as panic disorder, may be traced to similar stressors.

For an anxiety disorder known as post-traumatic stress disorder, the environmental second hit is the trauma itself—war, natural disaster, sexual assault. New research also indicates that obsessive-compulsive disorder, an anxiety disorder characterized by repeated, intrusive and unwanted thoughts and rituals, may occur in children with a genetic predisposition after they develop rheumatic fever. “In this case, the environmental second hit is the bacterial infection,” says Dr. Hyman.

To make more members of the public and health care professionals aware of depression and anxiety disorders and their effective treatments, NIMH conducts national education programs. These campaigns include community-based programs, public service announcements, publications, and audiovisual materials, many of them aimed specifically at women, advertising toll-free numbers that people can call to receive free information. If you think you or someone you know suffers from one of these disorders, call the following numbers:

Depression: 1-800-421-4211

Anxiety Disorders: 1-888-8ANXIETY •

Lynn J. Cave, technical writer/editor, National Institute of Mental Health.

Schizophrenia is a severe mental illness marked by hallucinations, delusions, thought disorder, flat emotional state, and lack of interest in surroundings. The disorder is no more common in women than men. However, women with schizophrenia are more likely to exhibit sadness, irritability, and anger, as well as more paranoia and explosivity. Men are more likely to be withdrawn and emotionally unexpressive.

In bipolar disorder, also called manic-depressive illness, a person experiences episodes of depression and mania. The latter is marked by abnormal elevation of mood, rapid thoughts and speech, irritability, increased sexuality, decreased need for sleep, and poor judgment. The course of bipolar disorder in women is characterized by more depressive and fewer manic episodes, and women are more likely to develop a form of the illness in which they cycle rapidly between states of depression and mania.

The eating disorders anorexia nervosa and bulimia affect so many more women than men that some media have done stories to remind people that men can have these disorders. The vast majority of those afflicted with eating disorders are adolescent and young adult women. Stringent dieting to achieve an “ideal” figure can trigger these disorders. Also, women pursuing professions or activities that emphasize thinness—like modeling, dancing, gymnastics, and long-distance running—are more susceptible to the problem.

In our society, it is women who are more susceptible to physical and sexual violence. During their lifetimes, about 22 million American women will have been victims of rape or attempted rape. Most of these assaults occur before age 18. Studies also indicate that up to 25 percent of women are abused sexually as children or adolescents. Rape and childhood sexual abuse substantially increase the risk for emotional problems, including depression, anxiety, post-traumatic stress disorder, suicide, and eating disorders, as well as problems such as headaches and irritable bowel syndrome. Preliminary research results indicate that treatment involving mentally re-experiencing aspects of the traumatic event in a safe environment can reduce acute and chronic post-traumatic stress reactions. •

HORMONES

MAY EXPLAIN

WHY MORE

WOMEN

THAN MEN

HAVE TMD

I N S E A R C H O F

Temporomandibular

A N S W E R S

Disorders:

Temporomandibular disorders (TMD), a group of often painful conditions that affect the jaw joint (temporomandibular joint) and chewing muscles, confound and frustrate patient and practitioner alike. Controversy surrounds virtually all aspects of TMD, from diagnosis and treatment to its prevalence and causes.

The good news is that for most people, pain in the area of the jaw joint or muscles is not a signal that a serious problem is developing. Generally, discomfort from TMD is occasional and temporary, often occurring in cycles. The pain eventually goes away with little or no treatment. Only a small percentage of people with TMD pain develop significant, long-term symptoms.

It is estimated that 10 million Americans experience TMD symptoms. TMD appears to affect women, particularly those ages 20 to 40, twice as often as men. A possible link between female reproductive hormones and TMD may help explain the disproportionate prevalence among women.

A recent study found that postmenopausal women receiving hormone replacement therapy were 70 percent more likely to experience TMD than women who did not take hormones. In a group of women ages 15-35, those using oral contraceptives were 20 percent more likely to have TMD. These

findings suggest that a women's own hormones also could increase her risk for TMD. More research is needed to substantiate the role of hormones in TMD.

CAUSES

Severe injury to the jaw or temporomandibular joint can cause TMD by disrupting the smooth motion of the jaw and causing pain or locking. Arthritis in the jaw joint may also result from injury. Other causes are less clear. Some suggest, for example, that a bad bite (malocclusion) or orthodontic treatment can trigger TMD, but recent research disputes that theory. Nor is there scientific proof that clicking sounds in the jaw lead to serious TMJ problems. In fact, jaw clicking is fairly common in the general population. If there are no other symptoms, such as pain or locking, jaw clicking usually does not need treatment.

Some experts suggest that stress, either mental or physical, may cause or aggravate TMD. People with TMD often clench or grind their teeth at night, which can tire the jaw muscles and lead to pain. It is not clear, however, whether stress is the cause of the clenching/grinding and subsequent jaw pain, or the result of dealing with chronic jaw pain or dysfunction. Scientists are exploring how behavioral, psychological, and physical factors may combine to cause TMD.

SIGNS AND SYMPTOMS

Pain, particularly in the chewing muscles and/or jaw joint, is the most common symptom of TMD. Others include limited movement or locking of the jaw; radiating pain in the face, neck or shoulders; painful joint clicking or popping; or a sudden change in the way the upper and lower teeth fit together. Headaches, earaches, dizziness and hearing problems may also be related to TMD. Researchers are working to clarify TMD symptoms with the goal of developing better and easier methods of diagnosis and treatment.

DIAGNOSIS

Because the exact causes and symptoms of TMD are not clear, diagnosing these disorders can be confusing. At present, there is no widely accepted, standard test to correctly identify TMD. In most cases, however, the patient's description of symptoms, combined with a simple physical examination of the face and jaw, provide enough information to locate the problem, make a diagnosis, and start treatment if needed. Sophisticated x-ray techniques may be needed only when a practitioner strongly suspects a condition such as arthritis or when significant pain persists over time and symptoms do not improve with treatment.

TREATMENT

Key words to keep in mind about TMD treatment are “conservative” and “reversible.” Conservative and reversible treatments are as simple as possible; do not invade the tissues of the face, jaw or joint; and do not cause permanent changes in the structure or position of the jaw or teeth.

Because most TMD problems are temporary and do not worsen, simple treatment will usually relieve discomfort. Self-care practices such as eating soft foods, applying heat or ice packs, avoiding extreme jaw movements and learning to manage stress can help ease symptoms. Other conservative treatments include physical therapy and short-term use of muscle-relaxing and anti-inflammatory drugs.

The health care provider may recommend an oral appliance to help reduce clenching or grinding. These plastic mouth guards should not cause pain or permanent changes in the bite.

Other types of treatments, such as surgery, are irreversible and result in permanent changes in jaw position or tooth structure. Surgery should be avoided where possible. When such treatment is necessary, the patient should fully understand the reason for the procedure, the risks, and other types of treatment that may be available. Other irreversible treatments designed to bring the bite into balance may be of little value and may even make the problem worse. These include orthodontics; repositioning appliances; and extensive occlusal adjustment, in which many teeth are ground down.

RESEARCH DIRECTIONS

To address the issues surrounding TMD, NIH convened a Technology

Assessment Conference on Management of Temporomandibular Disorders in April 1996. The 15-member panel recommended a conservative and reversible approach to treatment for the vast majority of patients with TMD. They noted that universally accepted, scientifically based guidelines for diagnosing and managing TMD are not available and, as a result, practitioners sometimes have employed a variety of unproven diagnostic and therapeutic approaches. Concerns about the safety and effectiveness of these approaches, as well as potential for harm, led the panel to recommend studies to assess their accuracy, reliability, and cost-effectiveness.

The panel concluded that there are questions about the effectiveness of most treatments now used for TMD and called for clinical trials to determine their safety and efficacy. In addition, the panel encouraged professional education to ensure proper and safe practice in the treatment of these disorders.

The National Institute of Dental Research supports an active research program into the causes, diagnosis, treatment and prevention of TMD. For more information, contact the National Oral Health Information Clearinghouse, a service of NIDR, at:

1 NOHIC Way
Bethesda, MD 20892-3500
Telephone: (301) 402-7364
TTY: (301) 656-7581
Fax: (301) 907-8830
E-Mail: nidr@aerie.com •

*Pat Sheridan, public affairs specialist,
National Institute of Dental Research.*



The rounded ends of the lower jaw called condyles glide along the joint socket when we open and close our mouths. A soft disc lies between the condyle and the temporal bone to absorb shocks to the joint from chewing and other movements.

LINKS TO NUTRITION AND HEALTH

TASTE

Taste plays a crucial role in regulating our ingestion of foods and beverages. We can commonly identify four basic taste sensations: sweet, sour, bitter, and salty. Deficits of these four basic taste sensations present serious problems because they can affect our desire to consume nutrients. For example, a taste deficit may lead to an unhealthy, dietary habit

such as excess salt consumption or it can be linked to diseases or disorders including head trauma, cancer, diabetes, and obesity.

The National Institute on Deafness and Other Communication Disorders (NIDCD) supports research at Yale Univer-

sity where scientists are investigating the genetic variation in taste ability among individuals and its relationship to eating behavior and nutrition. A simple taste test using a bitter substance called PROP (6-n-propylthiouracil) is providing an important key to understanding taste-nutrition links. People can be classified into one of three groups: nontasters, medium tasters, or supertasters of PROP. By applying a dye to the tongue, the taste bud pores become visible and can be counted. Results show that supertasters have many more taste buds than nontasters.

Women are more likely than men to be supertasters. Supertasters perceive more intense tastes from some bitter and sweet compounds than do nontasters. For example, caffeine, quinine, and ethanol taste more bitter while sugar and saccharin taste sweeter to a super-



A patient going through a series of tests to measure her ability to detect and discriminate tastes and odors.

Researcher at the NIDCD, Dr. Robert D. Smith, is studying the genetic variation in taste ability among individuals and its relationship to eating behavior and nutrition.

Taster. Research has shown that for prepubertal girls and postmenopausal women, liking for sweets is related to their abilities to taste PROP. Those who taste PROP to be the most bitter (and thus have the most taste buds) like sweets the most. However, for women in their childbearing years, this reverses: women who taste PROP to be the most bitter dislike sweets the most.

During the last decade, remarkable progress has been made in establishing the nature of changes that occur in the sense of taste with age. NIDCD-supported scientists at the Pennsylvania State University's Hershey Medical Center found that in a sample of elderly women, a greater ability to taste PROP also was associated with nutritional indexes (such as lower body mass) that indicate a low risk for cardiovascular disease. These examples show that taste sensitivity to PROP offers an important key to taste-nutrition links. One reason that the powerful connection between the sense of taste and nutrition has been hard to document in the past is the presence of taste disorders. The sense of taste can be altered by common medical problems (ear infections,

mild head injuries).

E Additionally, it has been found that supertasters experience the most intense tastes from a variety of sweet and bitter substances present in foods, as well as the oral burn from capsaicin (pronounced cap-SAY-iss-in), the active ingredient in chili peppers. Capsaicin burns most to elderly women supertasters, who might experience the greatest pain intensity since they have the greatest number of taste buds. They might even perceive unusually intense burning sensations because of the larger number of taste buds. The interaction of taste and trigeminal nerves may be one mechanism that can cause burning mouth syndrome in postmenopausal women.

Taste components, such as PROP receptors, may be estrogen-sensitive, and thus decline after menopause. The NIDCD supports research attempting to determine whether there are variations in taste ability and number of taste buds that can be related to variations in sex hormones, and research to understand the influence of drugs, hormone levels,

and other physiological variables on taste. This research is important because factors that affect taste can significantly influence nutritional intake and complicate clinical treatment.

NIDCD is one of the institutes of the National Institutes of Health. NIDCD conducts and supports biomedical and behavioral research and research training on normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language affecting 46 million Americans. NIDCD supports efforts to create devices that substitute for lost and impaired sensory and communication functions. NIDCD also conducts and supports research and research training that is related to disease prevention and health promotion. NIDCD achieves its mission through a wide range of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions and organizations. •

*Cheryl D. Fells, public affairs specialist,
National Institute on Deafness and Other
Communication Disorders.*

THIS RESEARCH IS IMPORTANT BECAUSE FACTORS THAT AFFECT
TASTE CAN SIGNIFICANTLY INFLUENCE NUTRITIONAL INTAKE
AND COMPLICATE CLINICAL TREATMENT.

CAMP CALCIUM:



Fun

IN THE NAME OF SCIENCE

Adolescent Girls are Focus of NIH- Supported Research

One of Laura Gordon's most vivid memories from summer camp is piling onto a bus with her fellow campers at 6 a.m., then driving to Indianapolis to spend almost 15 hours in a hospital. At the hospital the girls all had needles in their arms, "and everybody was sleeping with one arm straight up in the air because we couldn't bend our elbows," recalls Laura, now a freshman at Purdue University in West Lafayette, Indiana.

This may not seem like a typical summer camp experience, but then this wasn't a typical summer camp. Laura and 13 other 12- to 14-year-old girls were attending "Camp Calcium," a camp run by Connie Weaver, Ph.D., professor and head of the foods and nutrition department at Purdue. The main purpose of Camp Calcium is to find out how much calcium growing girls need to get in their diets so that they can develop the strongest possible bones, and thus help reduce their chance of getting osteoporosis later in life.

Osteoporosis is a disease in which low bone mass and deterioration of bone quality lead to reduced bone strength and an increased risk of fractures. It is the major underlying cause of bone fractures in postmenopausal women and the elderly. About 25 million people in the

United States have or are at risk of developing osteoporosis, and 80 percent of those affected are women. Osteoporosis is responsible for about 1.5 million fractures each year—most commonly of the hip, spine, and wrist. Osteoporosis of the spine can cause back pain, height loss, and a stooped or hunched posture.

The day the girls spent in the hospital was only one day out of their 3 weeks at camp. The rest of the time was spent in and around a sorority house at the Purdue campus. For three of the past seven summers, Weaver and her colleagues have rented a sorority house and moved in with anywhere from 14 to 37 adolescent girls. "We try to make Camp Calcium the best camp [the girls] could ever imagine going to," says Weaver, whose research on calcium is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. There are lots of typical camp activities, such as outings, arts and crafts, and sports. The girls also take classes on subjects such as computers, health, fitness, and nutrition. Hanging out at one of the scenic spots on campus to watch boys is a very popular camp activity. The camp also gives the girls a chance to see women scientists in action, and Weaver says some of the campers come in part

because they like the idea of contributing to women's health research.

Weaver and her colleagues recruit girls for Camp Calcium by visiting local middle schools, where they give presentations on calcium and bone health and hand out flyers about the camp. After she receives applications from those girls who are interested, Weaver holds an orientation for prospective campers and their parents. The girls and their legal guardians then sign consent forms saying that they understand what is involved and agree to participate in the medical studies at the camp.

CAMPERS' CALCIUM LEVELS MONITORED

One of the things that makes Camp Calcium different is that the girls have to eat a controlled, calcium-rich diet prepared by the camp dietitians. "They have to eat everything we prepare and nothing else," explains Weaver. To make sure the girls eat all their food, Weaver and the rest of the camp's staff members eat with the campers.

"We measure everything that goes in and everything that goes out" in terms of calcium, says Weaver. The girls often have their blood drawn before breakfast. They also have to collect

their own urine and fecal samples in special containers. The researchers then analyze the calcium content of all these samples and calculate how much dietary calcium got into the bloodstream, how much calcium was excreted, and how much calcium each girl retained. The girls who come to Camp Calcium don't really mind collecting the samples. "After you do it for a week, you get used to it," says Laura, who notes one benefit. "Now when I go to the doctor, I have really good aim!"

The body of an average adult contains about 1,000 grams (2.2 pounds) of calcium, 99 percent of which is found in the skeleton (bones and teeth). We take in calcium through our diet, and lose it from the body mainly in urine, feces, and sweat. Most dietary calcium is absorbed into the bloodstream in the small intestine. The body depends on adequate calcium from the diet both to build healthy new bone and to avoid excessive loss of calcium from bone.

The girls spend one day of camp at the hospital, where they get their bones scanned by a machine that measures bone density. At the hospital the researchers also give the girls two special, traceable forms of calcium and then draw their blood at regular intervals over a period of many hours. The researchers measure these calcium tracers in blood, urine, and fecal samples from subsequent days. The results of these studies show how much calcium is absorbed in the digestive tract, how the kidneys handle calcium, and how much calcium goes into bone. Even in fully grown adults, bone is constantly turning over and being remodeled, with old bone being removed and replaced by new bone.

After participating in Camp Calcium, the girls come back one day a year to give a blood and urine sample, fill out a questionnaire about their diet,

and get their bone density checked. Some of the girls also have come back for another full session of camp.

This lets the researchers find out what happens to calcium retention and bone mass in the girls over several years.

Some Food Sources of Calcium¹

400 mg	<ul style="list-style-type: none"> 3 1/2 oz sardines with the bones 8 oz plain, lowfat yogurt with added milk solids 8 oz plain, nonfat yogurt 4 oz tofu processed with calcium salts²
300 mg	<ul style="list-style-type: none"> 1 cup skim, lowfat, or whole milk, or lowfat chocolate milk 1 cup buttermilk 8 oz plain, whole milk yogurt 8 oz fruit-flavored, lowfat yogurt 1/2 cup part-skim ricotta cheese 1/4 cup instant, nonfat dried milk 1 cup cooked, drained collard greens, from frozen
200 mg	<ul style="list-style-type: none"> 1 oz cheese (cheddar, part-skim mozzarella, muenster, provolone, pasteurized process American or Swiss) 1 cup ice cream or ice milk 3 1/2 oz canned pink salmon with the bones 1 cup cooked, drained kale, from frozen 1 cup cooked, drained turnip greens (from raw/fresh or frozen)
100 mg	<ul style="list-style-type: none"> 3/4 cup lowfat (2%) or creamed cottage cheese 1 cup cooked, drained broccoli, from frozen 1 1/3 cup cooked, drained broccoli, from raw 3/4 cup cooked, drained collard greens, from raw 1 cup cooked, drained kale, from raw
50 mg	<ul style="list-style-type: none"> 2 oz canned, drained clams 3 oz canned shrimp or 4 1/2 oz steamed, fresh shrimp 2/3 cup oyster meat, raw (9-13 medium)

Note: People who cannot reach their optimal calcium intake by eating conventional foods can also meet this need with calcium-fortified foods (such as some fruit juices, fruit drinks, breads, and cereals) as well as calcium supplements.

¹ Source: Human Nutrition Information Service, U.S. Department of Agriculture. Numbers have been rounded slightly.

² Calcium content of tofu varies greatly. For information consult the label or the manufacturer.

RESEARCH SHOWS IMPORTANCE OF CALCIUM IN EARLY YEARS

The studies done by the Camp Calcium researchers are showing just how important it is for adolescent girls to get plenty of calcium in their diets. Other studies have shown that women acquire 91 percent of their skeleton by age 17, and 99 percent by age 26. "If you build more bone when you can, then you can afford to lose some without becoming at risk for fracture later in life," says Weaver. But just how much calcium is enough? And which are the most critical years for building new bone?

At the first Camp Calcium, in the summer of 1990, Weaver and her colleagues compared adolescent girls (ages 12 to 14), who were in the peak of their growth spurt, and young adult women (ages 19 to 30), who had achieved their full height, to see how they might differ in the ways their bodies handled the calcium they took in. Each of them took in about 1,300 milligrams (mg) of calcium each day through their diet.

The researchers found that at this level of calcium intake adolescent girls retain about 25 percent of the calcium they take in, while young adults retain an average of only 5 percent of dietary calcium. The girls retained more calcium than the women did through a combination of increased absorption, higher bone turnover, and lower excretion in the urine. "The kidneys of adults are not as efficient at retaining calcium," Weaver says. "Women over the age of 21 lose as much calcium as they take in. You can't build [much] more bone after that age."

Weaver's research shows that the peak age for calcium retention in girls is around the time when they start having menstrual periods. After that, the body's ability to retain calcium starts to decline. Other studies have shown that in the United States, on average, girls past the age of 11 start taking in less calcium in their diets, falling below the recommended intakes. This is around the very time that Weaver's studies show is critical for building bone. "We need to 'hit' girls [with the message to get enough calcium] right before age 11, when something is happening to make them decide they're not so interested in drinking milk and eating other calcium-rich foods," she says.

"After adolescence," Weaver says, "the goal has to switch from building bone to

Summary of Recommendations for Optimal Calcium Intake* Made by a Consensus Development Panel Convened by NIH

JUNE 1994

Age Group	Consensus Panel's Recommended Optimal Daily Intake (mg calcium)
Infants	
Birth - 6 months	400
6 months - 1 year	600
Children	
1 - 5 years	800
6 - 10 years	800-1,200
Adolescents/young adults	
11 - 24	1,200-1,500
Men	
25 - 65 years	1,000
Over 65 years	1,500
Women	
25 - 50 years	1,000
Over 50 (postmenopausal)	
On estrogens	1,000
Not on estrogens	1,500
Over 65 years	1,500
Pregnant and nursing	1,200-1,500

* Optimal calcium intake refers to the level of calcium consumption (from the diet plus supplements, if needed) that is necessary for a person to maximize their peak adult bone mass and then to maintain bone mass and minimize bone loss in later years.

retaining what you have." This doesn't mean that women over 21 shouldn't worry about getting enough calcium, Weaver cautions. "Calcium intake is important throughout life, but you lose your ability to acquire additional bone by late adolescence."

Studies done at the second Camp Calcium, in 1993, show that the optimal level of calcium intake for growing girls is somewhat higher than the current recommended dietary allowance (RDA) of 1,200 mg. The girls had to take in at least 1,300 mg of calcium each day, on average, for their bodies to retain the maximum amount of calcium.

In summer 1997, Weaver ran the first Camp Calcium for African-American adolescent girls. The purpose of this session is to find out whether there are differences in calcium retention between African-Americans and whites. Weaver believes there may be a difference because, on average, African-American women have a higher peak bone density and are less likely to suffer from osteoporosis.

Weaver says more and longer-term research is needed to find out whether opti-

mizing calcium intake in growing girls will enable them to attain a higher peak bone mass when they are fully grown. Some other, larger NIH-sponsored studies are underway to address this question. In the meantime, Weaver and her colleagues are answering other key questions on women's health. And some of the campers are learning important lessons about nutrition and health that will last a lifetime.

In addition to having fun and making new friends at Camp Calcium, Laura Gordon says, "I learned a lot about diet. I drink a lot more milk than I drink [soda] pop now. I used to drink pop in the morning, pop at night. I realized that's not very healthy for you." Recently Laura, who is 5 feet 9 inches tall, has noticed that her grandmother is losing height as a result of osteoporosis of the spine. "I'm trying to drink a lot more milk nowadays. . . because I don't want to be hunched. I like my height." •

Elia Ben-Ari, writer-editor/deputy information officer, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Preventing Osteoporosis...

WHY MILK MATTERS NOW FOR FEMALE TEENS

Soda, fries, and burgers. Typical teen cuisine.

Teens may not think much about what they eat. Or how what they eat today will affect them tomorrow, or twenty years from now. But over the last several decades, researchers from the National Institute of Child Health and Human Development (NICHD) have learned a great deal about how a nutritionally balanced diet during childhood and adolescence works to prevent the onset of damaging adult diseases.

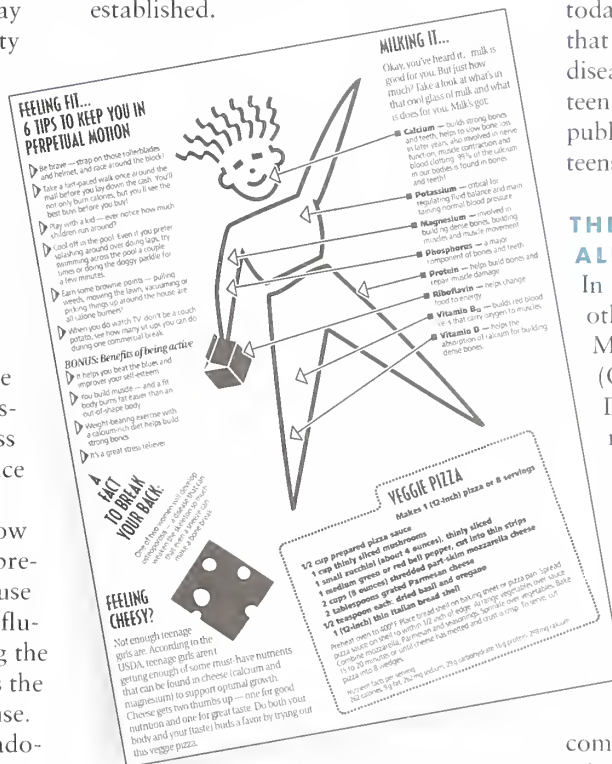
One long-lasting effect of nutritional imbalance during adolescence is osteoporosis, a bone-crippling disease characterized by low bone mass and an increased bone fragility. Once recognized primarily as an elderly woman's disease, osteoporosis is now being acknowledged as a partially preventable "adolescent" disease because the occurrence of osteoporosis is influenced by bone mass attained during the first three decades of life, as well as the amount of bone lost after menopause. An optimal calcium intake during adolescence, when 50 percent of adult skeletal mass is formed, decreases the risk of the crippling fractures caused by osteoporosis.

Attaining genetically determined peak bone mass is, truly, "kid-stuff," and a bit more. A recent NICHD-supported study found that calcium supplementation of the diets of girls, ages 12 to 16, produced a 14 percent increase in bone density in comparison to unsupplemented girls. Though seemingly minimal, the impact of this 14 percent increase in bone density is striking: for every 5 percent increase in bone density, the risk of fracture declines by 40 percent. And, by the time adolescents finish their "growth spurt" around the age of 17, approximately 90 percent of their adult bone mass will have been established.

But a recent national survey indicates that 85 percent of adolescent females do not consume the Recommended Daily Allowance (RDA) for calcium. Many adolescent females avoid dairy products, the best source of calcium, because of the perception that all dairy products are fat-laden foods. Other teens replace milk with regular or diet soda, unconcerned about the "empty calories" or limited nutritional value of soda. Some teens are not aware of the serious, long-lasting implications of inadequate calcium consumption. And most do not think they will ever become one of the 26 million women that suffer from osteoporosis today. NICHD is working to ensure that teens can avoid this bone-crippling disease by conducting research on the teen calcium crisis and developing a public health campaign to get female teens out of their calcium conundrum.

THE RECOMMENDED DAILY ALLOWANCE OF CALCIUM

In 1994, NIH, including NICHD and other institutes with the Office of Medical Applications of Research (OMAR), sponsored a Consensus Development Conference on Optimal Calcium Intake. The conference report recommended that young adult women, up to age 24, ingest 1,200-1,500 mg of calcium per day, slightly above the current RDA for female adolescents. The current RDA for adolescent females, 1,200 mg per day, was last calculated by the National Research Council's RDA Subcommittee in 1989. The RDA Subcommittee set the 1,200 mg per day RDA by extrapolating data from adult, not child-based, calcium studies, because so few studies of child calcium requirements



Public health campaign provides literature to encourage adolescent girls to increase their daily intake of calcium

had been conducted. The RDA Subcommittee is reviewing and updating the RDA for several vitamins and minerals, including calcium, and will now have available data from several large-scale studies of calcium requirements in children. One of these studies was conducted by NICHD-funded researcher Thomas Lloyd, Ph.D.

NUTRITION RESEARCH AT NICHD: FEMALE ADOLESCENTS AND THE CALCIUM CRISIS

At Pennsylvania State University, Lloyd studies the dietary, endocrine, and lifestyle factors that affect the acquisition of peak bone mass in female adolescents. Based on the results of recent placebo-controlled calcium supplementation studies, Lloyd found that calcium-supplementing the diets of girls ages 12 to 16 produced a 14 percent increase in bone density in comparison to unsupplemented girls. Lloyd also found that calcium-supplementing the diets of girls ages 14-16 produced more than twice the increment in bone density as those supplemented at ages 12-14, identifying the ages of 14-16 as a time of special concern for adding to bone density.

CALCIUM REQUIREMENTS DURING ADOLESCENT PREGNANCIES

Currently, there is no established Recommended Daily Allowance for calcium intake for pregnant adolescents. Logically, adolescents who become pregnant, nearly one million each year, need more calcium to maintain a positive balance for both themselves and their fetus. NICHD-funded researcher Jorge Prada, M.D., is evaluating the calcium requirement for pregnant adolescents, the role that calcium plays in bone metabolism, the incidence of hypertension, and the occurrence of pre-eclampsia, which is the development of dangerously high hypertension during pregnancy. Prada is currently recruiting pregnant adolescents between the ages of 12-20 to participate in the Randomized Calcium Trial in High Risk Pregnancies at the University of Cincinnati. His trial is the first U.S. study to address the calcium requirement of the pregnant adolescent.

THE ADOLESCENT FEMALE ATHLETE: DISORDERED EATING, AMENORRHEA, AND OSTEOPOROSIS

The competitive adolescent female athlete may often be at risk for developing this trio of medical disorders. The compounded effects of osteopenia (reduced bone mass), amenorrhea (loss of periods), and disordered eating can be debilitating for the female teen athlete. In fact, recent studies have shown that the spinal density of some young female athletes is similar to that of women in their 70s and 80s. Despite the fact that their weight-bearing exercise acts to increase bone density, this exercise often cannot compensate for the lower estrogen levels associated with menstrual dysfunction and the resultant loss of bone. NICHD-funded researcher Michelle Warren, M.D., medical director for the Women's Center for Health and Social Issues at St. Luke's-Roosevelt Hospital, studied the eating patterns of ballet dancers to determine if dietary patterns could account for the incidence of stress fractures. Warren found that stress fractures were significantly associated with a more restrictive diet. The majority of the dancers with recent stress fractures had weights 75 percent of their ideal weight, exhibited a high incidence of eating disorders, and had a low dietary fat intake. And, while many young female athletes may aspire to be "ultra-thin," the loss of 25 percent of total body weight causes serious physiological disturbances, like amenorrhea, which has been linked to increased stress fractures.

PUBLIC HEALTH IMPLICATIONS OF THE DECLINING CALCIUM INTAKE IN FEMALE ADOLESCENTS

Though the threat of osteoporosis may be in the far-off future for many female teens, NICHD recognizes the immediate need to reverse their inadequate calcium intake. NICHD is planning a public health campaign geared toward increasing their calcium consumption by encouraging them to consume nature's most calcium-rich food: milk.

The campaign will concentrate first on increasing the calcium intake of the most milk-averse teens, females ages 11-17, and then on younger girls, ages 6-11. The goal of the NICHD-proposed

THE NICHD CAMPAIGN WILL EDUCATE PARENTS AND PHYSICIANS ABOUT THE IMPORTANCE OF INCLUDING THE APPROPRIATE AMOUNT OF CALCIUM IN THE DAILY DIETS OF YOUNG CHILDREN AND ADOLESCENTS, AND EMPHASIZE THAT MILK CONSUMPTION IS A MUST DURING THE CHILDHOOD YEARS.

campaign is to increase the consumption of milk so that most female adolescents consume 1,200-1,500 mg of calcium per day, equivalent to approximately 4-5 eight-ounce glasses of milk. The NICHD campaign will educate parents and physicians about the importance of including the appropriate amount of calcium in the daily diets of young children and adolescents, and emphasize that milk consumption is a must during the childhood years.

An additional component of the campaign will be educating the nearly two million adolescent female athletes participating in interscholastic competition about the importance of an appropriate calcium intake. Because many female athletes are overtly "fat conscious," dairy products, often perceived as only fatty foods, are avoided. The campaign will seek to educate them on the effects of a dangerously low calcium intake, including the predisposition to stress fractures as teen athletes and the eventual onset of osteoporosis, and the availability of low-fat milk. The campaign will also concentrate on teaching the female adolescents who become pregnant each year about the greater need for calcium during pregnancy. •

Robin Petb-Pierce, writer/editor and NICHD coordinator, "Milk" Public Education Campaign, National Institute of Child Health and Human Development.

Alcohol Research and Alcohol

Women represent one-third of the estimated 14 million alcohol-abusing or alcohol-dependent people in the United States. Studies show that although women tend to drink less and generally have fewer alcohol-related problems than men, women who drink the most heavily equal or surpass men in the number of resulting alcohol-related problems. Women and men respond differently to alcohol: Women become intoxicated after ingesting quantities of alcohol smaller than those quantities needed to produce the same effect in men.

Several reasons may underlie this disparity:

- Women tend to have lower body water content and more fatty tissue than men of the same size. Because alcohol is more soluble in water than in fat and diffuses uniformly through all body water, the blood alcohol concentration (BAC) resulting from a given volume of alcohol is higher for women than for men.
- Activity levels of gastric alcohol dehydrogenase (ADH)—a stomach enzyme that breaks down alcohol—are thought to be lower in adult women than in adult men. Lower levels of ADH activity would allow more alcohol to be made available to women's body systems.
- Fluctuations in women's hormone levels during the menstrual cycle affect the rate of alcohol metabolism, re-

Alcohol Research and Alcohol Women's Health

sulting in higher BAC's at different points of the cycle.

Research also suggests that the existence of a genetically influenced form of alcoholism is as likely for women as it is for men. As in men, two types of alcoholism appear to occur in women: early onset and late onset. Early-onset alcoholism appears to be more genetic than environmental in origin, whereas late-onset alcoholism appears to be influenced more by environmental factors.

HEALTH RISKS

Women may be at greater risk than men for incurring alcohol-related problems. For example, female alcoholics have death rates ranging from 50 to 100

GENDER DIFFERENCES PLAY AN IMPORTANT ROLE

percent higher than male alcoholics; female alcoholics also are more likely to die from suicides, alcohol-related accidents, circulatory disorders, and liver disease. Correlations exist, too, between alcohol consumption and increased risk for problems such as breast cancer and reproductive disorders, as well as heart muscle and brain damage.

Women are at increased risk for alcohol-induced liver disease. Compared with men, women drinkers have a higher incidence of liver disease (e.g., cirrhosis of the liver or alcoholic hepatitis) even though they generally consume less alcohol for shorter periods of time. Differences in how men's and women's bodies process alcohol likely are responsible for the enhanced tissue damage suffered by women. Gender differences also may exist in the progression of alcohol-induced liver disease in women—evidence shows that injury to the liver advances more rapidly and is more likely to be fatal in women than in men.

Another area of research receiving attention is the possible link between alcohol use and breast cancer. The study of breast cancer's relationship to alcohol consumption is a new line of research, and the connection is yet unproven. Epidemiological research indicates that women who drink are approximately 1.2 to 2.0 times more likely to develop breast cancer than women who do not consume alcohol. More research is needed to determine whether alcohol consumption actually leads to breast cancer or whether other environmental variables, such as nutrition and diet, are the primary risk factors.

Long-term alcohol consumption also may disrupt the functioning of hormone-producing glands. For example, alcohol's interference with the hormonal regulation

of the reproductive system can lead to various reproductive disorders, including cessation of menstruation, irregular or absent menstrual cycles, painful menstruation, early menopause, and risk of spontaneous abortion. In addition, alcohol consumption during pregnancy can lead to a range of birth defects, including the most severe form, known as fetal alcohol syndrome.

A complex relationship exists between alcohol consumption and bone metabolism: At high levels of consumption, alcohol produces a deficiency of hormones that regulate calcium distribution, leading to a loss of calcium in the body. Calcium loss can lead to osteoporosis, a crippling disease that affects four to six million older Americans, primarily women. In its most severe form, osteoporosis leads to shrinking height, back pain, spinal deformity, and increased risk of bone fractures. However, low levels of alcohol consumption lead to an increase in estrogen production in postmenopausal women, actually decreasing the risk for osteoporosis as well as for coronary heart disease.

PREVENTION AND TREATMENT ISSUES

Efforts to prevent alcohol-related problems, as well as strategies to delay the onset of drinking or encourage abstinence, are aimed at both changing the individual's behavior and reshaping the environment (e.g., defining and governing appropriate drinking behavior and controlling alcohol availability). Researchers are exploring prevention efforts and intervention strategies that target women in general as well as specific groups of women (e.g., pregnant women, women who have been victims of abuse, and women of ethnic or racial minorities). The results of this research will enable us to design and implement more effective prevention programs.

Despite frequently reported barriers to treatment such as lack of child care,

about 25 percent of alcoholism clients currently in traditional treatment centers in the United States are women. Though women compose a seemingly small percentage of the treatment population, the proportion of female alcoholics to male alcoholics in treatment is similar to the proportion of all female alcoholics to male alcoholics. In addition to using traditional alcoholism programs, women tend to seek other methods of alcoholism treatment (e.g., psychiatric services or personal physicians). Research suggests that women who successfully complete treatment programs tend to have a slightly higher rate of abstinence than men.

Researchers are beginning to examine alternative treatment approaches specific to women and are providing valuable information for developing innovative treatment strategies. Although some approaches remain the same for both men and women (e.g., using naltrexone to prevent relapse and reduce alcohol craving), the causes and consequences of alcohol abuse and alcohol dependence may differ for each gender. Although men and women respond equally well to the same treatment approaches, gender-specific treatment may have advantages over mixed treatment settings. Current research is beginning to address these issues.

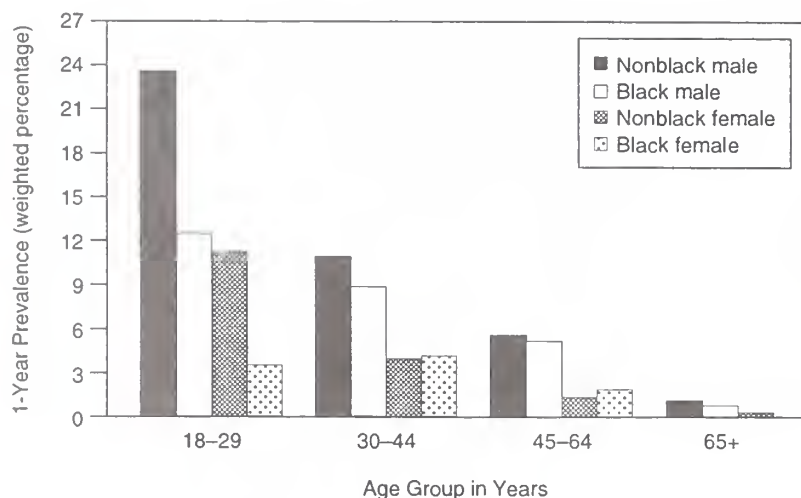


Figure 1 Prevalence of alcohol abuse and dependence by age, sex, and ethnicity in the United States, 1992, based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

SOURCE: Grant, B.F.; Harford, T.C.; Dawson, D.A.; Chou, P.; Dufour, M.; and Pickering, R. Prevalence of DSM-IV alcohol abuse and dependence: United States, 1992. *Alcohol Health & Research World* 18(3):243-288, 1994.

CONCLUSION

The past three decades have seen a steady increase in research on women's health and alcohol consumption. Contemporary studies no longer focus solely or disproportionately on men, and recent years have yielded significant research advances that have improved women's health. Although scientific research is providing answers to questions long posed, more research is needed on a broad range of topics, from the relationship between alcohol use and breast cancer to the

role of gender in treatment outcomes. The scientific community has contributed much to women's health research, yet much more remains to be accomplished. •

Jason M. Novak, writer, National Institute on Alcohol Abuse and Alcoholism.

RECOMMENDED READING

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- Lisansky-Gomberg, E.S., and Nirenberg, T.D., eds. *Women and Substance Abuse*. Norwood, NJ: Ablex Publishing, 1993

For more information on NIAAA publications, visit the NIAAA World Wide Web site at <http://www.niaaa.nih.gov>.

Beyond the Mammogram

BREAST CANCER SCREENING:



Woman receiving a mammogram

(Photo courtesy of the National Cancer Institute)

In the majority of cases (70 to 85 percent) where mammography shows a suspicious spot, a breast biopsy may be negative. Nevertheless, each year thousands of women experience weeks of emotional and physical discomfort before the uncertainty ends. Of course, if the biopsy is positive, a woman faces more surgery that involves not only the breast but often the lymph nodes under the arm to determine whether the cancer has spread. Then comes radiation or chemotherapy and more anxious waiting to see if the treatment will shrink the tumors.

To speed up this process and make the procedures less invasive, researchers at two research centers supported by the National Center for Research Resources (NCRR) are using positron emission tomography (PET) and magnetic resonance imaging (MRI) to diagnose and evaluate breast cancer and to monitor its treatment.

Dr. Mitchell Schnall, chief of the University of Pennsylvania Hospital's magnetic resonance imaging section in Philadelphia, is exploring the use of MRI as an alternative to breast biopsies. Collaborating with researchers at the NCRR-supported Metabolic Nuclear Magnetic Resonance (NMR) Research Resource (also at the University of Pennsylvania), Dr. Schnall and his associates

used MRI to analyze suspicious breast lesions. In one study, they used MRI to evaluate lesions that had shown up on mammograms of 167 women. Based on the mammogram results, these women had biopsies that revealed 57 cases of invasive cancer and 15 noninvasive tumors. MRI done before the biopsies detected all 57 invasive tumors and 9 of the 15 noninvasive tumors. And in 22 patients, MRI found additional tumors that hadn't shown up on mammograms.

MRI "SEES" HARD-TO-FIND TUMORS

According to Dr. Schnall, MRI is extremely sensitive to cancer. "With MRI you see cancer that is very hard to see by other techniques," he says. Other research suggests that MRI is nearly 100 percent sensitive to cancer.

But sensitivity is only part of the picture. For diagnosing cancer, a method must not only find all the cancer, it must not mistake anything else for cancer. This discrimination is known as high specificity. To determine MRI's specificity, doctors inject the patient with a contrast agent—a material that travels through the body and shows up clearly

OTHER TECHNOLOGIES FOUND TO BE EFFECTIVE

on the images. "We take high-resolution images before and after we inject the contrast agent, and we see where the contrast goes," explains Dr. Schnall. "The agent tends to go to areas that have more blood vessels, which tend to be the tumors." He says the images produced by MRI show the tumors in vivid detail.

Although thousands of hospitals across the country already have MRI units, MRI is still an expensive way to image breasts compared to mammography. Nevertheless, Dr. Schnall believes the technique eventually may have a strong role in evaluating suspected breast tumors and planning treatment. It may prove especially helpful for women whose mammograms are difficult to interpret because of surgical scars, breast implants, or dense breast tissue. MRI might also help surgeons pinpoint the extent of cancer prior to surgery and sort out which women need mastectomies and which would be good candidates for breast-conserving treatments, such as lumpectomy and radiation.

At the NCRR-supported General Clinical Research Center at the University of Michigan Medical Center in Ann Arbor, PET plays a similar role. In one branch of research there, Dr. Richard L. Wahl, professor of internal medicine and radiology, and his colleagues are



Dr. Mitchell S. Schussman uses magnetic resonance imaging (MRI) to detect and evaluate breast tumors. MRI may eventually be used as an alternative to breast biopsy.



In pilot studies, Dr. Richard L. Wahl determined that positron emission tomography (PET) could show if breast cancer had spread to the underarm lymph nodes.

using PET to determine if breast cancer has spread to regional lymph nodes. Currently, the only way to know if breast cancer has spread is to surgically remove the underarm lymph nodes and examine them under a microscope.

Many women object to the surgery because it may cause lasting discomfort, swelling, and restricted arm movement.

In PET, doctors inject glucose labeled with a small amount of radioactivity into the patient. After about an hour, the labeled glucose accumulates in tissues that use more glucose—such as breast tumors. The PET scanner, which is sensitive to small amounts of radioactivity, produces images that show these concentrations of labeled glucose.

EARLY STUDIES SHOW PET CAN DETECT CANCER IN LYMPH NODES

In pilot studies, Dr. Wahl and his colleagues found that PET could detect large primary breast tumors and show whether the cancer had spread into the underarm lymph nodes and other parts of the body. Convinced of the method's feasibility, the researchers now are trying to determine the size of the smallest tumors PET can detect.

They also want to know if PET can

be as effective as lymph node surgery in detecting the spread of cancer, and whether it can predict which women need further treatment, such as chemotherapy.

In a 5-year multicenter clinical trial that has just begun—funded with more than \$4 million from the National Cancer Institute—Dr. Wahl and colleagues at Duke University in Durham, North Carolina, and Washington University in St. Louis, Missouri, plan to do PET scans of 430 women who have been diagnosed with breast cancer and are scheduled to have lymph node surgery. In addition to scanning the patients' underarm lymph nodes, the researchers will scan lymph nodes behind the breast bone. In some cases, these nodes are better than underarm nodes for revealing if cancer has spread. After the women have had both PET scans and lymph node surgery, researchers will compare results.

Their hope, Dr. Wahl says, is that PET eventually can substitute for lymph node biopsy. "The PET machine in its current form is not a microscope, and it's not equivalent to microscopic examination of the nodes," he says. "But the resolution of PET scanners is improving, and we think that we'll increasingly be

able to see smaller nodal abnormalities."

The researchers will track all the women to find out whether their cancers return. This information will show whether PET can be used to predict a patient's outcome.

In other studies, Dr. Wahl is looking at PET's role in monitoring patients' responses to chemotherapy. The usual way to gauge response is to watch for changes in tumor size. But it may take weeks or months for tumors to start shrinking. PET can detect responses much earlier because it measures tumor metabolism, which starts changing almost immediately if chemotherapy is successful. If PET shows that chemotherapy isn't successful, the treatment can be quickly changed to another form, sparing the patient extra weeks of side effects from an ineffective treatment. •

*Kathy Kaplan, public affairs specialist,
National Center for Research Resources.*

The work described in this article was supported by the National Center for Research Resources and the National Cancer Institute.

Knowledge

Is Improving

Power:

Women's

Health with

Technology

WOMEN'S HEALTH HAS BECOME A TOPIC OF INCREASING INTEREST TO THE NATIONAL INSTITUTES OF HEALTH, AND RIGHTLY SO.

FEMALES COMPRISE 51 PERCENT OF THE U.S. POPULATION, ACCORDING TO THE CENSUS BUREAU. GIVEN WOMEN'S HIGHER LIFE EXPECTANCY, THAT NUMBER WILL CLIMB AS THE "BABY BOOM" BECOMES THE "SENIOR BOOM" NEXT CENTURY.

THE NATIONAL LIBRARY OF MEDICINE (NLM) STRIVES TO IMPROVE WOMEN'S HEALTH IN TWO WAYS: GETTING ACCURATE, UP-TO-DATE MEDICAL INFORMATION INTO THE HANDS (OR ON THE COMPUTER SCREENS) OF WOMEN EVERYWHERE AND TO HEALTH PROFESSIONALS AND RESEARCHERS OF BOTH GENDERS WHO CARE FOR AND CONDUCT STUDIES ABOUT WOMEN. ADVANCES IN TECHNOLOGY HAVE MADE A RICH NEW BODY OF INFORMATION ON WOMEN'S HEALTH AVAILABLE WITH UNPRECEDENTED EASE TO A WORLDWIDE AUDIENCE, AS THE FOLLOWING EXAMPLES ATTEST.

THE BODY ELECTRIC: *The Virtually Endless Possibilities of the Visible Woman*

"We hold these truths to be self evident, that all men and women are created equal."

—Elizabeth Cady Stanton at the first Woman's Rights Convention, Seneca Falls, New York, July 19-20, 1848

Although feminist Stanton spoke wisely about women's right to *political* equality with men, her statement would not apply to their bodies. This is borne out by NLM's "Visible Human Project," in which the woman is "more equal" than the man.

With this ambitious undertaking, NLM sought to produce full-color, three-dimensional, computer-generated images of two bodies, one male and one

ADVANCEMENTS PROVIDE GREATER ACCESS TO MEDICAL INFORMATION

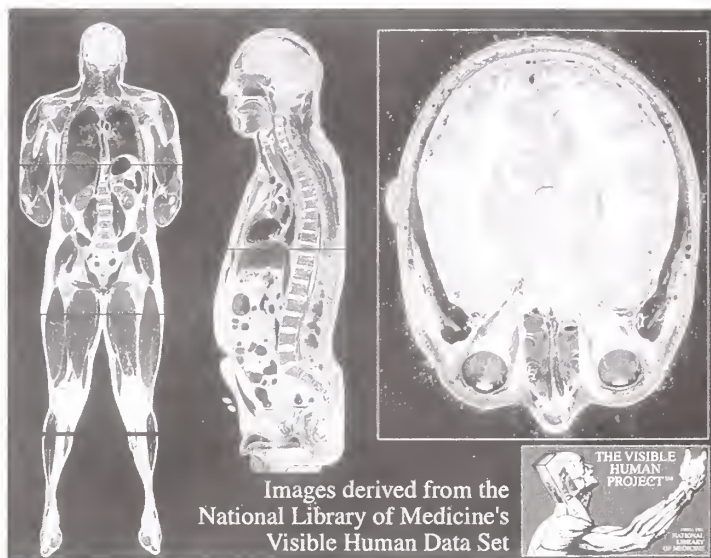
female. An anonymous 59-year-old Maryland woman is now immortalized in cyberspace as the "Visible Woman."

Her body was imaged from head to toe using computed tomography (CT), magnetic resonance (MR) and X-rays. Next, it was embedded in blue gelatin, frozen, and sliced crosswise into more than 5,000 pieces, each one-third of a millimeter thick. Each slice was digitally photographed.

Besides the obvious differences between the anatomy of the Visible Man, launched on the Internet in 1994, and the Visible Woman, released the following year, there's another key difference: from her data, one can produce images that are three times sharper than those of her male counterpart.

"We demanded more of our technology and ended up with a significantly higher resolution for the Visible Woman than we achieved for the Visible Man," explains NLM Director Donald A. B. Lindberg. "This is vital because the data can then be reformatted to show additional information with even more detail. Medical professionals can study the Visible Woman data to learn more about female anatomy, perform better surgical planning, continue training, and conduct research."

Since the Visible Human datasets were made available to the public, NLM has awarded more than 650 licenses for their use to persons in 26 countries. Innovative researchers, physicians, computer scientists, and others have developed the following applications of the data, among many others: (1) "surgery simulators" for physicians that, like flight simulators for pilots, let them practice procedures repeatedly on computer before entering the operating room; (2) "The Dissectable Human," a CD-ROM that allows viewers to study the organs and systems of the body in 3-D. Already in use at medical schools, it's revolutionizing the teaching of anatomy; and (3) "virtual colonoscopy," a non-invasive colon



Images from the Visible Woman

cancer screening method. In time, it could eliminate the need for the current invasive procedure, which is costly and uncomfortable.

The Visible Humans delineate the differences between the male and female anatomies and offer dazzling new perspectives on each. Both are available under a license agreement from NLM at no charge over the Internet or on magnetic tape. For more information on the Visible Human Project, consult NLM's World Wide Web home page: <http://hvwv.nlm.nih.gov>, or send a fax to the Visible Human Project office, 301-402-4080.

INTERNET GRATEFUL MED: A World of Information on Women's Health

"When you educate a man you educate an individual; when you educate a woman you educate a whole family."

—attributed to Charles D. McIver, in a speech at North Carolina College for Women

For years, health professionals have used it to make diagnoses, develop treatments, and keep up with rapidly changing therapies and technologies. Medical students have relied on it for their studies. As of April of 1996, the general public, via the World Wide Web, has had access to more than eight million references and abstracts of medical literature from 4,000 journals, dating back to 1966. This up-to-date gold mine of information is called

MEDLINE. It's a product of the National Library of Medicine and is the world's largest medical database.

Although initially intended for health care providers and biomedical researchers, MEDLINE, which went online in 1971, is becoming popular with a growing number of consumers. One reason for this is the Internet Grateful Med, a system that allows anyone with Internet access and a World Wide Web browser to search MEDLINE easily. As a result, physicians are finding their patients increasingly well-informed by the medical materials they can access with a few clicks of the mouse.

Jean Hoffman-Anuta, a pharmacist from Millersville, Maryland, put Internet Grateful Med to work with exciting results. After having one healthy

child, Jean and her husband, Michael, experienced six consecutive first-trimester pregnancy losses. Using Grateful Med to search MEDLINE, they pinpointed several articles with information that ultimately led to a full-term pregnancy and a healthy son, Sam.

Ms. Hoffman-Anuta told a medical audience in Washington, DC, "To everyone responsible for Grateful Med, we would just like to let you know that our family will be eternally 'Grateful' for Sam!"

For information on how to search MEDLINE over the Internet, visit the Internet Grateful Med web page at <http://igm.nlm.nih.gov>. •

Melanie Modlin, public information specialist, National Library of Medicine.



Baby Sam (left) and his dad, Michael Anuta, and big brother Michael look on as mom Jean Hoffman-Anuta uses a laptop computer to connect to the Internet Grateful Med. Sam is truly a child of the Computer Age.



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